Every case of Congenital Syphilis is a failure of Syphilis Control"

THEODORE J. BAUER, Medical Director
Chief, Division of Venereal Disease

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CONGENITAL SYPHILIS

By

DAVID NABARRO

M.D F.R C.P

Consulting Pathologist formerly Director of the Pathological Department and Medical Officer in charge of the Venereal Diseases Clinic (1917 1939) at the Hospital for Sick Children, Great Ormond Street London



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PREFACE

NOWADAYS so little is heard of congenital syphilis in Britain that some explanation of the publication of a volume upon the subject seems to be called for. When, in 1916, it was decided to start venereal diseases clinics in Britain, a clinic for children to be run at the Hospital for Sick Children, Great Ormond Street, was included in the scheme. I became the first director of the clinic, in addition to being the hospital bacteriologist. The clinic was started on January 1st, 1917, mainly at first as an outpatient department and from 1923 onwards with the addition of two small wards for gonococcal and syphilitic patients. Shortly after the outbreak of war in 1939 the clinic was closed down. During the 23 years of its existence records were obtained of nearly 900 cases of congenital syphilis and an additional 150 cases of probably or possibly congenital and acquired syphilis in infancy and childhood. The result was that I became interested in several side issues of the disease, which have been elaborated in this book to an extent unusual in a treatise on congenital syphilis: for example, the relation of congenital syphilis to cardiovascular disease, to herpes polio-encephalitis, parotitis and possibly other virus infections, to lymph-node enlargement and to syphiloids. Congenital neurosyphilis from its prevalence and resistance to treatment has received full consideration.

The prevalence and intensity of the disease have diminished to such an extent in Britain and other equally fortunate countries that my theses can no longer be put to the test in them, but it may prove possible to do so in other countries. Even in the less enlightened parts of the British Commonwealth and Empire infantile congenital syphilis still occurs and may yet survive for years, so that an account of its symptomatology during the past 50 years in Britain may be of value, since it may resemble the local type of the disease in many respects. For this reason and since the book is a historical record of the disease as seen in Britain in the pre penicillin era, many cases have been recorded in considerable detail for future comparison and reference. It must be remembered, however, that the rapid action of penicillin can produce more dramatic immediate effects than arsphenamines or bismuth, since penicillin can be given in more effective doses without giving rise to toxic effects. We have still to learn what the remote effects of penicillin on the disease will be 20 or 30 years hence. Even here in Britain we must not be too complacent, for whereas both the prevalence and the severity of infantile congenital syphilis have been declining over a number of years, the incidence of cases of the disease in older children has not diminished to nearly the same extent, which seems to show that many infantile cases escape detection through

having been rendered very mild or even latent. Judging from the attitude of teachers of medicine surgery and particularly of paediatrics, who in my opinion take too rosy a view of the situation, congenital syphilis will not be eradicated in this country for many years.

Among the remedies I venture to suggest are the following (1) Integrating the teaching of venereal diseases with that of medicine surgery obstetrics paediatrics and antenatal pathology and hygiene. (2) Cultivating a higher index of suspicion for syphilis which would lead to requests for more serological tests to be carried out. (3) Admittedly treatment is much better now than it was 30 or 40 years ago, but I would not yet rely solely upon penicillin penicillin alone and the combined treatment suggested on p 417 might be tried in parallel series of cases and then followed up for as long as possible from the point of view of cardiovascular neurological ophthalmic and other manifestations of late syphilis, in addition to the serological reactions

ACKNOWLEDGEMENTS

In a work like this based on more than 30 years of clinical study and in which so many colleagues co-operated it is inevitable that my list of acknowledgements is long and that several collaborators have passed on I sincerely thank all my colleagues for having entrusted their patients to me for treatment. In particular I must mention my indebtedness to the late A. T Pitts, dental surgeon and the late Bertram Shires radiologist to the hospital Our discussions contributed to our knowledge of the teeth and bone lesions respectively in congenital syphilis, as did those with W H McMullen, P G Doyne G G Penman and J H Doggart on the eye lesions Of my junior colleagues clinical and pathological, I would thank especially Drs. B B Sharp A. G Signy and W W Payne Successive matrons, almoners and nurses J Wickliffe Peck, honorary consulting pharmacist to the hospital, his successor and assistants have all earned my gratitude for the help they afforded me

It is a pleasure to put on record my gratitude to Miss M M Irving sister in-charge of the clinic and wards from 1925 till 1939 for her unselfish devotion to duty and for the unremitting care and attention she bestowed upon the children entrusted to her To Miss E. Campbell, my secretary and technical assistant from the inception of the clinic until my retirement grateful thanks for loyal service are due The former hospital secretary the late James McKay and the present secretary and house governor Mr H F Rutherford are warmly thanked for their co-operation in the working of the clinic and for their perennial interest in the patients The Superintendent of the School for the Blind at Swiss Cottage N W 3 and Dr Steele his medical officer co-operated loyally for several years by sending suitable residents of the school for treatment some of whom benefited to such an extent that they were no longer considered sufficiently incapacitated to be residents of the institution.

To the London County Council I am indebted for facilities granted me by the creation of a congenital syphilis unit in one of its hospitals

Thanks are also due to the editors of the *American Journal of the Diseases of Children* the *American Journal of Pediatrics* and the *American Journal of Syphilis Gonorrhoea and Venereal Diseases* for permission to quote from McLean s Whipple and Dunham s and Hinrichsen s articles, to Messrs J and A. Churchill for permission to reproduce Hutchinson s original account of interstitial keratitis to Methuen and Co to use Bishop Harman s chart on p 34, to Messrs. E. and S Livingstone for permission to use Figs. 76 and 77 and to Mr Johnston Abraham for permission to quote from his Vicary Lecture and to reproduce the portrait of Fracastor lent by Messrs. J Wright of Bristol. I am indebted to Prof H. E. Sigerist for the loan of his print of Paracelsus, which Dr Ashworth Underwood, of the Wellcome Historical Medical Museum, kindly photographed for me, as he also did Figs. 4, 5 6 7 8 9 10 11 12 13 and 15 For that valued assistance Dr Underwood has my warmest thanks For the use of Fig. 9 I thank Mr Otto Glasser and Messrs. Staples Press Ltd. The photograph of Prof Levaditi is by Gourast. I am indebted to Mr Peter Cull, the medical artist at the Hospital for Sick Children for Figs 18 19 89 and 93

A few special acknowledgements are reserved for the end

Mr Derek Martin, Assistant Curator of the Museum at the Hospital for Sick Children, to whom my debt of gratitude is great, came to my department as technician in 1924 and from that time onwards his services have been of the utmost value both to the hospital and to me. His post mortem work, his photography and his microscopy have all been of a uniformly high order and but for them this work could not have appeared in its present form. Mr Martin is responsible for most of the photographs and photo-micrographs and for the staining of the sections I ask him to accept my warm appreciation of his valued help

The Medical Research Council and the Ministry of Health are thanked for financial aid on two separate occasions for secretarial service and to the Board of Management of the Hospital I am particularly indebted for financial help in seeing the book through the press. It is essentially a Great Ormond Street book on congenital syphilis as the work was mainly carried out there and its publication has been generously financed by the hospital, but for the views expressed therein I alone am responsible

My son, Dr John Nabarro has helped me in many ways for which I cannot thank him sufficiently for without that help and without constant exhortation from my wife and friends who have been interested in the production of the book, it would not have come to fruition.

In conclusion I must thank my publishers most cordially for their forbearance at all times.

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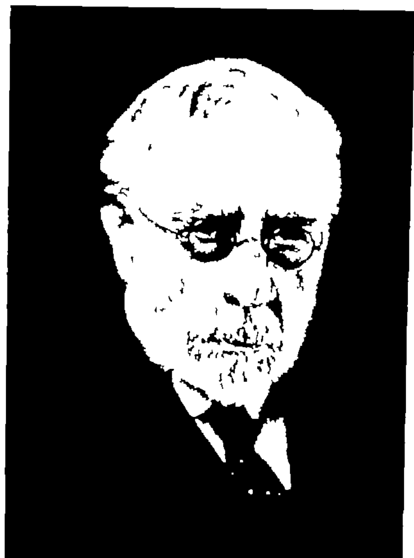
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Thos Barlow

FIG 1 Sir Thomas Barlow Bt K.C.V.O. M.D., F.R.S

CHAPTER 1

DEFINITION OF TERMS AND NOMENCLATURE

SYPHILIS contracted by an infant before birth has received several qualifying names. The two best known are congenital and hereditary syphilis, which for many years have been used interchangeably by authors, though admittedly neither term is entirely satisfactory

Congenital syphilis (from the Latin *congenitus* born with) implies that the disease was present at birth, just as congenital dislocation of the hip congenital heart disease or any other congenital anomaly would be, but it does not imply that the parents, and almost certainly the mother must themselves be syphilitic and have transmitted the infection to their child. The other congenital defects listed above are all acquired *in utero* but are not necessarily present in the parents.

The name hereditary or inherited syphilis implies that the disease has been inherited from the parents and, in that respect, is an improvement on the name congenital syphilis but it is commonly held that, in the genetic sense, an infectious disease cannot be inherited It is pointed out, however in Chapter 4 that there may be rare instances of hereditary transmission in third-generation syphilis or of an ovum being infected before or after conception, and possibly developing normally though probably abnormally (see also Whipple and Dunham, 1938).

On reviewing the literature of the subject since the beginning of this century it is remarkable what different concepts are included in the terms employed. Carpenter (1901), in an interesting monograph on syphilis in children, used the terms congenital and hereditary interchangeably for that form of the disease which is conveyed *in utero* from the parents to the child. It is so named, he says, to distinguish it from the acquired form, which is rarely met with in infants and children. G F Still (1908) also uses the terms inherited and congenital syphilis synonymously and he does not include in this category the rare cases in which the disease may be contracted during birth from a syphilitic sore on the maternal genitalia. He remarks that the term infantile syphilis would therefore include more than inherited or congenital syphilis Some writers (Diday Fournier *et al*), Still adds, have sought to make a distinction between the words inherited and congenital, using inherited to indicate that the syphilitic infection took place at the time of conception,

and congenital to indicate conveyance of the disease during some later period by infection of the mother during pregnancy L. W Harrison *has consistently from 1918 onwards called the disease congenital syphilis* Browning, McKenzie and Watson (1912–1933) have also used the term congenital syphilis without any reservations, Watson alone commenting that the use of the term inherited syphilis is scientifically unsound.

Findlay (1919) wrote Uterine infection is often spoken of as congenital or hereditary syphilis according as to whether the child is born with or without symptoms of the disease. The two terms are however frequently used synonymously In all cases the child is infected before birth sometimes early in foetal life, sometimes late, and probably not infrequently during parturition. Of the two terms, congenital syphilis is decidedly the better

Kolmer (1920) introduced the term prenatal syphilis (*prae-natalis* before birth), which has been adopted by Stokes and other American and British authors.

The Solomons (1922) used the term congenital syphilis to denote the infection of offspring which occurred *prior to* or *during* birth. The term hereditary syphilis *they used in the restricted sense to indicate changes* in the offspring due, not to active and direct infection with the treponema but to germinal defects caused by parental syphilis.

David Lees (1927) in the first edition of his book used the terms congenital and inherited syphilis synonymously In the second edition (1931) the chapter on congenital syphilis was headed inherited syphilis, and the third edition (1937), which was edited by Robert Lees and others, retains the term inherited syphilis for the headings of the chapter and its paragraphs, but in the text sometimes uses the term congenital

Jeans and Cooke (1930) use the terms congenital and hereditary syphilis interchangeably remarking nevertheless that both terms are open *to objection. They do not approve of the use of the term hereditary* syphilis for the lesions of occult or para syphilis as has been done by the Solomons and many French authors, because, they say even if it could be proved that the alleged germinal defects were due to parental syphilis, the term would be misapplied for the reason that these children do not have syphilis. They gave the title Prepubescent Syphilis to their book.

Melgrave (1931) writes A disease such as syphilis can never be congenital in the truest sense. This term should be applied only to primary diseases which so far as our present knowledge goes are inseparably associated with the germ-plasm of the individual He says the term *congenital syphilis should be given up as being a relic of the days when* the causal organism was as yet undiscovered The disease acquired by the foetus *in utero* he calls antenatal syphilis and for the infection acquired in labour during the transit of the foetus through the birth pas-

stages he suggests the term "con natal syphilis." In both cases it is an acquired disease said Melgrave. Eric Pritchard commenting on this suggestion, pointed out that the term "con-natal" might be ambiguous used in this sense, for one dictionary meaning of the word "con natal" was *born with*, so that the term "con natal" might quite well be applied to an infection contracted *in utero* Pritchard suggested "intranatal" for an infection conveyed during birth

Tytler Burke (1940) objected to the use of both terms "congenital" and "hereditary" syphilis, which in his opinion should be discarded. The disease cannot be inherited in a biological sense and is acquired by the foetus. He used the name "prenatal syphilis," as also does McLachlan (1944).

The majority of French authorities use the terms "hérédo-syphilis" or "syphilis héréditaire," thereby emphasizing the transmission of the infection from parents to offspring It is the opinion in this and most other countries that the French have exaggerated the rôle of syphilis in the causation of disease in children, for many and varied congenital anomalies and dystrophies have been attributed to the effects of the treponema or its toxin upon the child's germ-plasm, the child exhibiting none of the ordinary symptoms or signs of congenital syphilis and having a negative blood reaction. As will be mentioned shortly there may be something to be said in support of the thesis of syphilitic dystrophies, to which the younger Fournier devoted a monograph in 1898 This work commended itself to J W Ballantyne, the great exponent of ante natal pathology and hygiene.

The older German authorities used the terms "kongenitale syphilis" and less frequently "hereditäre syphilis." The monograph on this disease in Jadassohn's "Handbuch der Haut und Geschlechts-krankheiten" (1927) is entitled "Kongenitale Syphilis," but more recently Erich Hoffmann has advocated the name "angeborene syphilis." C. Goedhart, of The Hague, has adopted this term in his monograph on the disease and its prevention (1941). Previously (1930) Hoffmann had suggested the name "innate syphilis" (*lues innata*) and in the address referred to stated that Spiethoff had named the disease *syphilis connatalis*

The term "congenital syphilis," despite the objections which have been raised against it, is so well established in the literature that it is probably the best name for the disease. Until a true hereditary transmission of syphilis from parent to offspring has been scientifically proved it will be better not to give to the disease the name of "inherited or hereditary syphilis." There are, admittedly many gaps in our knowledge of its aetiology The actual cause is undoubtedly the *Treponema pallidum*, but whether the spirochaetal form of the parasite is the only or even the most important, phase in its life-cycle, or as various authorities aver there is a granule or even an ultramicroscopic stage of the parasite, is still shrouded in mystery (Levaditi *et al*)

Infection of the ovum may take place at the time of conception and develop for a time *pari passu* with the embryo This possibly leads in most cases to early death of the embryo and its expulsion by abortion. On the other hand the parasite or its toxin may affect the developing embryo at a rather later date, and should this occur before the end of the second or third month of pregnancy it might conceivably give rise to congenital defects and anomalies—mental as well as physical—as E. Fournier Ballantyne, Still and many others have claimed. These older writers were of the opinion that other noxious influences such as tuberculosis, alcoholism lead poisoning and so forth might similarly affect the developing embryo during the first six weeks of intra-uterine life or subsequently during the foetal stage. The attention which has recently been drawn to the baneful effect of an attack of german measles and probably of other virus infections in early pregnancy has revived interest in the dystrophies and congenital malformations which writers had attributed to parental syphilis. The lesions produced will naturally depend *inter alia*, upon the stage of development reached by the embryo or foetus when the toxin acts. It is important to bear in mind that *infection* of the embryo by the treponema is not essential its toxin alone might be responsible for the mischief done, so that the foetus, should it survive, would show no direct evidence of syphilis. To this condition the name occult or para syphilis may in my opinion, be appropriately applied. The syphilitic origin of such cases will often remain undiscovered unless the possibility of its occurrence is borne in mind and a painstaking history of the parents and even of the grandparents is obtained. These relatives should whenever possible have a physical examination, including a serological blood test.

If infection takes place still later in the pregnancy let us say after the fourth month, which is said to be the earliest time that spirochaetes can be demonstrated in the foetus, the parasites may multiply to such an extent as to compass the death and expulsion of the foetus in the form of a miscarriage, or foetal death may be caused by syphilitic disease of the placenta. Should infection occur still later in the pregnancy the effects might be less severe, so that the foetus is not destroyed until the seventh or eighth month of intra uterine life, to be born a week or two later as a macerated foetus. On the other hand, a late intra uterine infection may allow a syphilitic child to be born apparently quite healthy the symptoms and signs of congenital syphilis only becoming manifest after a latent period of several weeks or the symptoms may not appear for years or the disease may remain latent until it is discovered accidentally by blood test during the routine investigation of an infected family

Cases of infection have been recorded as having occurred during parturition (' intranatal, Pritchard) through contact with a sore on the mother's genital passage. Exceptionally a primary chancre on the

infant's body may testify to such a mode of infection. These intra natal infections, which are very uncommon resemble the acquired syphilis of childhood or adults, inasmuch as the swarming of the parasites and the pathological changes in the organs, which are so characteristic a feature of congenital syphilis, would not be present in anything like the same degree.

We are in complete ignorance of the conditions which determine the stage of pregnancy at which the ovum or foetus becomes infected or why some infections are so much more severe than others or why some syphilitic mothers may bear syphilitic children alternating with healthy ones. The following family affords an instance of this

Family 705

Father History of primary syphilis 1919. 2 years' treatment at hospital X. W R. negative in 1934 at hospital Y

Mother Said to have had secondary syphilis 3 months after marriage and to have had 6 months treatment at hospital X. In 1933 the W R. was strongly positive at hospital Y

Eight pregnancies

1 (before marriage) F with no infantile symptoms and said to be well at age 10 years (not seen).
2. F 1926 A year after marriage and after mother had had 6 months treatment. The child made slow progress in infancy W R. + +[1] at 7 years.
3 F 1927 "Healthy baby Latent syphilis at 7 years. W R. + +
4. M. 1928. No infantile symptoms. Fits of temper W R. 4 × 4,[1] that is strongly positive, at 6 years.
5. M. 1929. No infantile symptoms. Rickety W.R. negative at 5 years
6 F 1930. No infantile symptoms later bow-legged and not thriving W R. 4 × 4 at 4 years.
7 M. 1931 No infantile symptoms. Rickety W R. negative at 3 years.
8. M. 1938. After 5 months treatment during pregnancy at hospital Y mother defaulted. W R.? Patient died of "broncho-pneumonia" at 5 months.

We have seen that congenital syphilis may be present for several months during pregnancy or may manifest itself at very varying times after birth. Accordingly the following forms of the disease may be recognized

(1) Foetal or antenatal syphilis this is nearly always fatal.
(2) Neonatal manifesting itself a few days after birth this, too is nearly always fatal.
(3) Early infantile, the symptoms beginning at the age of 4 to 6 weeks.
(4) Late infantile, apparently starting at 9 to 12 months. It is possible that cases falling into this category are relapses or recurrences ("recidives")—the earlier manifestations having been so slight as to have been overlooked or forgotten.

[1] For the meaning of these symbols see p 81 under W.R.

(5) Late (tardive) congenital syphilis or *lues congenita tarda*, the symptoms of which may start as early as 3 years or even before, and at the other extreme may not become manifest until the fourth or even the fifth *decade* of life.

(6) Lastly there is a considerable group of cases to which the name latent, asymptomatic or unrecognized congenital syphilis has been given.

Cases falling into the categories (5) and (6), although they may occur during childhood or adolescence may not be diagnosed until adult life has been reached.

During the course of one s study of patients suffering from syphilis or being members of a known syphilitic family one has encountered cases of the following different types

(*a*) Undoubted cases of congenital syphilis belonging to one or other of the six groups enumerated above.

(*b*) Cases which I designate probable or *b* cases for example, a child born immediately before or after a known syphilitic one, who showed signs or symptoms of the disease in early life but is either dead or not available for present examination.

(*c*) A type *c* case only possibly syphilitic, such as a miscarriage or a premature stillbirth just before or after a known syphilitic child.

In addition three further categories were noted

(*d*) Normal, healthy children

(*e*) Cases of acquired or possibly-acquired (?*e*) syphilis in childhood and lastly

(*f*) Cases of occult or para syphilis, which might include such conditions as epilepsy chorea, mental defects, endocrine disorders resulting in infantilism, Fröhlich s syndrome, diabetes and so forth, occurring in children of syphilitic parentage. It is possible, too, that congenital malformations, dystrophies of various kinds and obscure anaemias may have resulted from parental syphilis in the past, though many will not agree with me on this point. Perhaps we shall now have no means of solving this problem, since penicillin *is able to deal the treponema of syphilis* almost a knock-out blow and so possibly may prevent these long term, remote effects.

In spite of the doubts cast upon this last group of cases, and of the objection raised by Jeans and Cooke and others, that such cases are *not* syphilitic, I believe they form an important group among the diseases of children and should be carefully studied. If syphilis be the cause—even though it may only be the indirect cause—of such conditions as may be included in this category it may act in two ways, either separately or jointly If it acts early in pregnancy it may interfere with the proper

development of the ovum and foetus, and give rise to malformations of various kinds much as rubella has been shown to be capable of doing If it acts a little later it may lead to congenital heart disease or other congenital malformations. Disordered functions may give rise to obscure anaemias, endocrine disturbances, epilepsy and other mental and psychic phenomena. It cannot be too strongly emphasized that these dysfunctions or dyscrasias, which some of us ascribe to the indirect action of the treponema, can frequently only be tracked down by a careful inquiry into the history of the child's parents and grandparents and, if possible, a physical examination including a serological blood test of as many members of the family as can be induced to respond

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CHAPTER 2

HISTORICAL

THE early history of syphilis is well told by Johnston Abraham in his Vicary Lecture for 1944. The disease was apparently unknown in Europe until the return of Columbus from America in the years 1493 and 1494, and it broke out like a plague in Italy in 1495. It spread rapidly to adjacent countries and was hence called by various names of which the most common was Morbus Gallicus, the French Disease. It was not



FIG. 2. Fracastorius

until Fracastorius published his poem Syphilis sive Morbus Gallicus, in 1530, that the name syphilis had ever been heard of. It was an invention of Fracastor himself intended to take the stigma from Italy as well as from France. According to the story a shepherd in Hispaniola, Syphilus by name, offended Apollo by refusing to make sacrifices to the sun god. For this *act of disobedience the shepherd was stricken with the disease* which has ever since been known by the name Syphilis.

Shortly after the alleged introduction of syphilis into Europe by the crews of Columbus, the occurrence of the disease was recognized in newly born infants, for as early as 1498 Torella mentioned its existence in the offspring of syphilitic parents. He and other contemporary writers thought the infection was conveyed during parturition or possibly through the mother's infected milk. Paracelsus (1493–1541), in 1529, appears to have been the first to assert positively the hereditary nature of the disease, for he recognized it at birth, thus showing that it must have been contracted *in utero*. His actual words "fit morbus hereditarius et transit a patre ad filium," reflect the common opinion of the time that the father was directly responsible for the child's infection, as the mother frequently appeared



FIG 3 Paracelsus

to be healthy. Ferrier (1553) went further and stated that the noxious agent could be attached to the paternal or maternal germ-cell; he also recognized a post-conceptional transmission of the disease.

Sir Frederick Still tells us that Simon de Vallambert in 1565 produced the first book on paediatrics written in French, a sign that the authority of the ancients, which had held sway for so long and incidentally had hampered the development of medicine as well as of knowledge generally, was at last beginning to be undermined. He was the first writer on the diseases of children to include a chapter on syphilis, and he quotes the case of a man who suffered from the "Great Pox" (syphilis) 14 or 15 years previously and "without his wife showing any signs of ill health begot children who all had the disease at 7 or 8 days old and gave it to their nurse."

Ambroise Paré (1510–1590) and others of that period recorded the infection of wet nurses by syphilitic infants and of healthy infants by syphilitic nurses. For nearly two centuries the main interest in congenital syphilis centred around the mode of origin whether the child was infected by the father or by the mother (*per generationem*) or by both whether the infection occurred during parturition or subsequently via the mother's milk or lastly through an infected wet nurse. It was not until 1722 when a posthumous book on the diseases of children by Christopher von Hellwig was published, that any real progress was reported. We learn from Still that Hellwig recognized the possibility of infantile marasmus being the only symptom of an otherwise latent syphilis. He described as symptoms Blisters in the mouth little swellings on the gums and on other parts of the body and, if the child has inherited the disease from the mother a rash between the legs The disease, he said, might also be conveyed by kissing The *inherited* disease is of worse prognosis than the *acquired* and in the former case the infant must not be suckled by the mother as it will only imbibe more of the disease. He recognized the danger of the infection of a nurse by a syphilitic infant, and on the whole, he concluded it is safest to abandon suckling altogether for these infants and to feed them on goat's or cow's milk. He advised the application of mercury ointment and giving a decoction of sarsaparilla.

Other writers of this period were Boerhaave (1668–1738) and Van Swieten (1700–1773) The former described the clinical course of syphilis and so anticipated by more than 100 years the more complete work of Ricord. The latter introduced liquor hydrarg perchlor (Van Swieten's mixture) for the treatment of syphilis. They both held the view that it was possible for the infection to be conveyed from father or mother to the offspring *per generationem*.

Likewise did Jean Astruc (1684–1766) who published books on venereal diseases (1736) and on diseases of women (1761). In 1746 an English edition of his lectures on diseases of children was published anonymously in London Still writes One might have expected that he would have had some original observations to offer on the *lues venerea* in children he does not even mention its occurrence. Nor is Diday much more impressed when he describes Astruc's book on the venereal diseases as an erudite and profound dissertation, but confined to recognizing and specifying the different share of the father and mother in the contamination of their progeny and to exaggerating the value of indirect treatment.

Rosen von Rosenstein (1706–1773), in his book on the Diseases of Children and their Remedies, gives a detailed account of the symptoms of congenital syphilis, including a good description of the early skin lesions. He also refers to a case of late congenital syphilis—a girl 11 years old, who had necrosis of the palate and nasal bones, ulceration of the face and enlargement of the cervical glands. He records the observations which are,

or should be, common knowledge to-day that in a syphilitic family healthy children may be born between infected ones and that syphilitic children may suffer in both body and mind. Mercury was used extensively in the treatment of syphilis in his day and von Rosenstein recommended mercury rubbings for the expectant mother to safeguard her child.

John Hunter (1728–1793) held that it was only the primary lesion which was infective and consequently he did not admit the possibility of intra uterine transmission of the disease to the infant. In his view infants who showed signs of congenital syphilis shortly after birth must have been infected during their passage through the genital canal from a local primary lesion. It may be recalled that in 1767 Hunter inoculated him self on the prepuce and glans with pus from a case of acute gonorrhoea, which gave rise to a chancre as well as to constitutional syphilis. From this and further experiments he concluded that a *single* venereal virus could be transferred to the urethra and other mucous membranes as gonorrhoea, or to the skin as a chancre, but that the blood and secretions of syphilitic patients were incapable of transmitting such contagion. He denied the intra-uterine transmission of syphilis and the possibility of extragenital infection as by kissing or by the use of contaminated instru ments, drinking vessels, etc. The knowledge of visceral syphilis which had been laboriously built up by Morgagni and others during the previous 250 years he brushed lightly aside by his casual observation I have not seen that the brain heart, stomach, liver kidneys and other viscera have been attacked by syphilis, although such cases have been described by authors. So great was Hunter s reputation that this remark was sufficient to cause visceral syphilis virtually to disappear from the text books on venereal diseases for more than 50 years, and likewise influenced the views of physicians and syphilologists upon the mode of transfer of the virus in the congenital disease.

An important impetus to the study of venereal diseases in mothers and infants was given by the establishment by Lenoir of a special hospital in Paris for the reception and treatment of venereally infected expectant mothers and their offspring This was about 1780 and in a book published in 1810, Bertin, one of the physicians to the hospital, gives an illuminating account of the good work carried out within its walls, and in particular of the reduction in the mortality rate among the newborn chil dren. It is interesting to read that all the contemporary physicians regarded ophthalmia as being one of the most frequent symptoms of venereal disease in infants, and all the symptoms as being due to one cause—namely syphilis. Bertin appears to have been a keen and accurate clinician, for he gives a detailed account of the symptoms of venereal disease as recog nized by him—the various lesions of the skin and nails, affections of the mucous membrane of the eyes, nose, urethra and anus, buboes and bone

lesions He lays particular emphasis on ophthalmia, which he says is often serious and may end in blindness. He recognized and described a case of periostitis in an infant 5 weeks old and its successful treatment with mercury He disputed Hunter's claim to have produced chancres by inoculating pus from a recent gonorrhoea, as he himself tried this experiment several times without success. These and other observations quoted in his book show that Bertin made a solid contribution to the contemporary



Fig 4 Abraham Colles

knowledge of congenital syphilis which has not received the recognition it merits

The Dublin surgeon Abraham Colles (1773–1843) wrote a treatise on syphilis based on his wide experience of the disease in which he made several important observations. These are so frequently misquoted and misinterpreted that it has been considered desirable to reproduce some of his original statements

I have never seen or heard of a single instance in which a syphilitic infant (although its mouth be ulcerated) suckled by its own mother had produced ulceration of her breasts whereas very few instances have occurred where a syphilitic infant had not infected a strange hired wet nurse, and who had been previously in good health (p 285)

It is a curious fact that I have never witnessed nor ever heard of an instance in which a child deriving the infection of syphilis from its parents has caused an ulceration in the breast of its mother. After citing a case which apparently formed an exception to this dictum, but which on closer study was found not to do so, he adds: This case shows that parents, who are not at all conscious of any derangement of health, may yet produce a child which shall, in a few weeks, exhibit the genuine characteristics of venereal disease, necessarily derived from one or both parents. Colles also noted that a man with latent, symptomless syphilis could infect his wife, so that secondary symptoms appeared in her without previous primary manifestations,[1] and that parents with latent syphilis could produce syphilitic children.

He concludes his chapter on syphilitic infants with the following dictum: One fact well deserving our attention is this—that a child born of a mother who is without any obvious venereal symptoms, and which, without being exposed to any infection subsequent to its birth, shows this disease when a few weeks old, this child will infect the most healthy nurse, whether she suckle it, or merely handle and dress it; and yet this child is never known to infect its own mother, even though she suckle it while it has venereal ulcers of the lips and tongue. Baumès made a similar observation in 1840, apparently independently of Colles' publication. To this dictum Jonathan Hutchinson gave the name Colles' law,[2] which Rietschel regards as the only important observation which has stood the test of time of all that was written in the nineteenth century about the transmission of parental syphilis. Colles himself made no attempt to explain the facts; our subsequent knowledge has confirmed his observations and to a considerable extent supplied the explanation of them.

Philippe Ricord (1800–1889), by his long study of the venereal diseases, re-established the foundations of scientific syphilology to which the teaching of John Hunter had given so severe a setback.

His most important contributions to our knowledge were his conclusive re-demonstration of the specific nature of syphilis and its separateness from gonorrhoea, and of the frequent co-existence of the two infections. He elaborated the work of Boerhaave by dividing the clinical course of syphilis into the three stages, primary, secondary and tertiary. For a long time he held the view that the primary stage was alone infectious, but in 1859 he was a member of the French Commission which reported upon the infectivity of the secondary lesions.

In addition to providing his own important contributions to our knowledge of these diseases, Ricord stimulated the study of syphilis in France which resulted in the formation of the two great French schools of

[1] It is now believed that in many instances there may be a chancre of the cervix uteri (Anwyl-Davies).

[2] In some Continental countries it is known as the Colles–Baumès law.

syphilology—that of Alfred Fournier in Paris and of Diday in Lyons. Rudolf Virchow (1821–1902), basing his work on the scientific foundations laid by Ricord wrote a treatise (1858) on the nature of the constitutional manifestations of syphilis, thereby throwing a new light on the periods of latency and recrudescence. P Diday (1812–1894) and his pupils concerned themselves chiefly with the problems of congenital syphilis, and in his book published in 1854 we find a full description of the infantile symptoms, except for the bone lesions, which he says are extremely rare in infants. According to Diday 6 months is the latest age at which a congenitally syphilitic child may show constitutional symptoms, and he is



FIG 5 Philippe Ricord

sceptical of the existence of the *lues congenita tarda* of some authors, as these, he says, are all more or less subject to doubt.

Sir Jonathan Hutchinson (1828–1913) stands out as the foremost British authority on syphilis in the nineteenth century He studied all aspects of the disease, but his most important observations were made in connection with the congenital form for (1) he established the fact that interstitial keratitis, which until then had been known as strumous corneitis, was practically always due to congenital syphilis (2) he was the first to describe the characteristic pegged and notched incisor teeth which are now known by his name and (3) he pointed out that interstitial keratitis and notched incisor teeth were frequently associated with 8th nerve deafness—the three signs being known as the Hutchinsonian triad From the year 1852

onwards Hutchinson wrote about these eye and teeth lesions in late congenital syphilis, but his teaching took a considerable time to influence Continental syphilologists, for we find that Robert in his "Nouveau Traité," which was based on work done in Ricord's clinic and which was published in 1861 makes practically no mention of the manifestations of late congenital syphilis. Hutchinson also drew attention to the occurrence of hydrocephalus and of iritis in syphilitic infants and he forestalled Kassowitz by 11 years in noting (1865) that the effect of parental syphilis



FIG. 6 Sir Jonathan Hutchinson

upon children became progressively weaker with the birth of each succeeding infant. This observation, to which exceptions may not infrequently occur is, however now generally known as Kassowitz law

Hutchinson's first paper dealing with infantile iritis, was published in 1852 when he was only 24 years old. Thereafter he wrote upon many branches of medical knowledge. The last edition of his work on syphilis was published in 1909 57 years after his first paper He was a keen observer an able clinician and an indefatigable worker

Jonathan Hutchinson, Jr (1859–1933), shared his father's interest in

syphilis and contributed articles on syphilis and gonorrhoea to Sir Frederick Treves' System of Surgery; but apart from a paper on the syphilitic diseases of joints, he did not make any important addition to our knowledge of the disease.

Although Bertin had described a case of bone disease in a syphilitic infant in 1810, it was many years before bone lesions were recognized as being of importance in the symptomatology of congenital syphilis. Diday in 1854 had written that bone lesions were extremely rare in infants, but in 1870 Wegner published his classical account of syphilitic osteochondritis in Virchow's *Archives*. Two years later Jules Parrot (1829-1883)



Fig. 7. Jules Parrot

published in the *Archives de Physiologie* his memoir on "Pseudo-paralysis caused by an alteration of the bones in congenitally-syphilitic infants." He made a careful study of the bones in syphilitic foetuses and young infants and came to the conclusion the bones were affected in nearly every case of congenital syphilis. It is of historic interest that the Museum of the Hospital for Sick Children, Great Ormond Street, London, possesses a case containing a number of Parrot's original preparations which he presented to the hospital. In addition to the changes in the long bones he described the changes in the skull bones now known as Parrot's nodes. Owing to the frequent association of rickets and congenital syphilis, Parrot taught that rickets was *always* caused by congenital syphilis, and so great

was his reputation in France and, through Sir Thomas Barlow also in England that this hypothesis of Parrot was generally accepted in the two countries. It was, however contested by Cozzolino Hochsinger and other Continental writers, and afterwards English and French authorities gave up Parrot's extreme view upon the subject.

Jean Alfred Fournier (1832–1914) shares with Sir Jonathan Hutchinson the distinction of being the greatest syphilologists of the nineteenth century He was an assistant to Ricord and devoted the whole of his



Fig 8 Alfred Fournier

professional life to the study of syphilis with its many facets. His first paper on the infectivity of the chancre, was published in 1857 then followed one on the incubation of syphilis in 1865 and one on the gummatous syphilide of the soft palate in 1868 Several of his courses of lectures were edited by his disciples (Pickard, Dreyfous and Brissaud) on syphilis of the testis in 1875 tertiary syphilitic epilepsy in 1876 pseudo-general-paralysis of syphilitic origin in 1878 and cerebral syphilis in 1879 Fournier emphasized the importance of thorough treatment long after the disappearance of symptoms in order to consolidate a cure and to safeguard any future children. In his work on Syphilis and Marriage (1880) he was the first syphilographer to give definite suggestions as to when it

might be considered safe for a treated syphilitic person to marry In his various lectures he emphasized the importance of syphilis as a cause of degenerative changes, especially in the cardiovascular and central nervous systems. For many years (1878–1894) he taught that the parasyphilitic affections—tabes dorsalis and general paralysis—were dependent upon antecedent syphilis, but it was several years before his views on this subject received general acceptance He continued to write various monographs on late congenital syphilis (1886), tertiary syphilis (1901) (edited by his son Edmond) on prophylaxis (1903), on treatment (third edition, 1909) and finally in 1910 a small monograph On the prevention and treatment of congenital syphilis—four mistakes to be avoided so that, as was the case with his contemporary Jonathan Hutchinson, his active literary life extended over a period of more than 50 years. Furthermore, in both cases the sons followed in their fathers footsteps but whereas the younger Hutchinson made of syphilis a subsidiary object of study Edmond Alfred Fournier (1864–1938) devoted most of his energies to congenital and third generation syphilis, upon which he wrote several monographs Stigmates dystrophiques de l'hérédo-syphilis (1898) Hérédo-syphilis de seconde génération (1905) Recherche et diagnostique de l'hérédo-syphilis tardive (1907) and Syphilis héréditaire de l âge adulte (1912). It must be unique for a father and son to have written books and articles on a single disease during a period of nearly 60 years.

Jonathan Hutchinson and Alfred Fournier were great friends and admirers of each other s work Hutchinson dedicated the last edition of his work on syphilis (1909) to Fournier whereas the latter in his publications, frequently referred to writings or quoted cases of my friend Mr Hutchinson

Sir Thomas Barlow (1845–1945) was the author of several interesting publications in connection with congenital syphilis (list on p x), and it was as a careful observer and skilled clinician that his great qualities became known to many generations of students whom he taught the art of observing for themselves. He was also a great humanist, which was obvious from the manner in which he dealt with his patients, adults as well as children. Barlow was a distinguished physician and was honoured by three British sovereigns who entrusted their health to his care. He was likewise one of the foremost paediatricians of the nineteenth century and it is of interest to record that at the Third International Paediatric Congress which was held in London in 1933 Sir Thomas Barlow then aged 88, attended the demonstration of cases which was given at the Hospital for Sick Children, Great Ormond Street. With his marked Lancashire accent, he eagerly discussed many of the cases in a manner which showed that he was mentally as alert as ever Many of the foreign, and even some of the English, members of the Congress had to be told who the distinguished old gentleman was, and most of them were amazed when

they learnt that it was *the* Dr Barlow who in the year 1883[1] had first described infantile scurvy —*die Barlow'sche Krankheit*—and in 1888 published his translation of Raynaud's eponymous essays on Local Asphyxia and Symmetrical Gangrene of the Extremities which were originally written in 1862 and 1874. To them he appeared to be an almost legendary figure.

The author had the good fortune to come under the influence of Sir Thomas Barlow in the year 1895 and in consequence owes him a deep debt of gratitude for the sound principles and wise teaching he imbibed from his preceptor He has endeavoured to repay this debt, though how inadequately he is painfully aware, by dedicating this work, by permission to the memory of Thomas Barlow

Quite early in his career Barlow became interested in congenital syphilis which was then a much commoner disease than it is to-day and he maintained that interest practically to the end of his long life. He was an ardent supporter of schemes for combating venereal disease and in his 70th year he was elected Chairman of the Executive of the National Council for Combating Venereal Disease, later the British Social Hygiene Council

In January 1877 there appeared his first paper on Enlargement of the spleen and heart disease in congenital syphilis," which sign Barlow tells us is not referred to by either Diday or Hutchinson in their writings Gee had drawn attention to splenomegaly in infantile syphilis in 1867 and stated that he had noted its occurrence in about half his cases Barlow thought that Gee rather underestimated its prevalence, for he himself found the spleen enlarged in 22 out of 28 cases. He noted too that when both liver and spleen were enlarged, the liver began to diminish in size before the spleen.

In the same year he reported two interesting cases of congenital syphilis —one showing meningitis, choroiditis and cerebral arteritis the other exhibiting gummata on several of the cranial nerves, disease of the cerebral arteries (one middle cerebral artery and the vessels constituting the circle of Willis), and cicatrices of the liver and spleen. This was apparently the first case of congenital syphilis to be recorded with gummatous cranial nerves, but, according to Barlow the arterial changes had previously been described by Heubner (1874) in cases of acquired syphilis Actually syphilitic arteritis with dispersed granulomata in the brain had been described six years previously (1868) by Clifford Allbutt. Both Allbutt's and Heubner's descriptions of syphilitic arteritis concerned adults with presumed acquired syphilis Barlow's cases in a 10-months and a 16-months-old child respectively were apparently the first recorded cases of syphilitic arteritis in the congenital disease. The arterial changes are

[1] "On cases described as acute rickets which are probably a combination of scurvy and rickets, the scurvy being an essential and the rickets a variable element." *Med Chir Trans London* (1883) 66 159



Fig 11 Erich Hoffmann



F 12 August von Wassermann

first in apes and later in rabbits and mice. In 1905 Schaudinn (1871–1906) and Hoffmann (b 1868) discovered and described the causal organism of syphilis, to which the name *Spirochaeta pallida* was originally given. Afterwards, to conform with priority of nomenclature Schaudinn renamed the parasite *Treponema pallidum*.

In 1906–7 Wassermann (1866–1925) Neisser and Bruck applied the complement fixation test of Bordet (b 1870) and Gengou (b 1875) to the diagnosis of syphilis, and evolved a practical diagnostic test for the



Fig 13 Paul Ehrlich

disease which is now widely known as the Wassermann reaction (W R.) or in several Continental countries as the Bordet Wassermann reaction (B W R.). The spirochaetal nature of syphilis established by Schaudinn led to the application of the brilliant researches of Ehrlich (1854–1915) in chemotherapy to this disease. After many compounds had been synthesized by Ehrlich and Hata, the 606th was tested by Alt in human syphilis and its therapeutic value established in 1910 This substance Ehrlich named salvarsan and he hoped that one big dose of the drug would kill off all the spirochaetes and thus eradicate the disease—the *therapia sterilisans magna*" This hope was unhappily not fulfilled

nevertheless the discovery of "606" (now renamed arsphenamine) inaugurated a noteworthy advance in the treatment and prognosis of the disease.

Many syphilologists on both sides of the Atlantic could be named as having made important contributions to one or more aspects of the disease, but only a few of them can be referred to by name A. S. Warthin who devoted years of work to the pathological aspects of acquired and con



FIG 14 L. W Harrison

genital syphilis J. W. Williams, J. H. Stokes, J. E. Moore, J. F. Mahoney Bauer Brown and Pearce Eagle, Kahn and a host of other American workers Hutinel, Jeanselme, Péhu Hochsinger Jadassohn and many other continental authorities Mott, Anwyl Davies David Lees, King Burke, McElligott and others of British nationality whose names will be found in the references to ensuing chapters in this book. There is, however one Englishman who has devoted practically his whole professional life to various aspects of the disease and by his many international contacts is known to practically every syphilologist throughout the

civilized world. I refer to Col L. W Harrison (b 1876) who began his close connection with venereal diseases as bacteriologist to the Military Hospital at Rochester Row London, in 1909

Early in his career Harrison joined the Royal Army Medical Corps, where he came under the influence of Almroth Wright, who stimulated in him the flair for and intimate knowledge of pathology which later pervaded all his work. He saw service in South Africa and India before becoming bacteriologist at Rochester Row Here he worked at the pathological diagnosis of venereal diseases including the improvement of the Wassermann technique, with the result that during the 1914–1918 war he became responsible for the diagnosis and treatment of venereal diseases in the Army wherever the forces were stationed. His concern for the proper treatment of merchant seamen and for the recording of their blood tests led to his suggestion in 1921 to the Congress organized by the League of Red Cross Societies that serum tests practised in the principal laboratories of the world should be compared, and the reports so drafted that they would be understood by clinicians everywhere He was a member of the League of Nations Health Organization which organized the serum conferences at Copenhagen and Montevideo. An important outcome of this work was the establishment in this country of a reference laboratory for the comparison of serum tests and the supervision of our V D clinics and laboratories.

After the 1914–1918 war he was appointed Adviser in Venereal Diseases to the Ministry of Health and for some years was the Director of the clinic at St. Thomas's Hospital. As adviser to the Ministry of Health, Harrison supervised the V D clinics throughout the country and thus became personally acquainted with, and friendly adviser to the heads of all the clinics. He has written several important text books and his contributions on Syphilis to the Medical Research Council's System of Bacteriology (1931) and to the British Encyclopaedia of Medical Practice (1939 and 1952) are authoritative and informative monographs. He was a founder and for several years President of the Medical Society for the Study of Venereal Diseases (M.S S V D) and also a founder and for many years the senior editor of the *British Journal of Venereal Diseases*

The history of Harrison's humanitarian work on venereal disease is told in an article in *Medicine Illustrated* from which it will be seen that it has hardly received in Britain the recognition it deserves The American Social Hygiene Association in 1946 awarded him the William F Snow medal for Distinguished Service to Humanity—a high honour indeed—which had only once before (in 1941) been awarded to a citizen of this country Mrs. Neville Rolfe, who was for many years the energetic secretary of the British Social Hygiene Council

Two other men of unusual ability must be named, though neither of them is a professed venereal diseases expert. They are Sir Alexander

Fleming Emeritus Professor of Bacteriology University of London, and Principal of the Wright Fleming Institute of Microbiology St. Mary's Hospital Medical School and Dr Thomas Parran Dean of the Graduate School of Public Health, University of Pittsburg Pennsylvania.

Alexander Fleming (b 1881) was another of Almroth Wright's pupils and he started to work in Wright's laboratory at St. Mary's Hospital almost from the time of his qualification. Inspired by the genius of his master he was not long in acquiring unusual manipulative dexterity and



Fig 15 Sir Alexander Fleming

keen power of observation Early in his career he devised a method for performing the Wassermann test using minute volumes of blood he also worked on Wright's opsonins and other protective substances in the body he discovered and named the lysozyme of the tears and later he discovered and named penicillin. It says much for Fleming's genius for critical observation that many of us had worked in bacteriological laboratories for years and must have had innumerable culture plates contaminated with moulds including Penicillium, but he was the first to realize the significance of the action of penicillin upon bacteria and its potentialities.

The discovery of penicillin by Fleming in 1928 and its development by Florey and his associates as a powerful chemotherapeutic agent during the

1939–1945 war were the means of saving countless lives. For this gift to mankind Fleming deserves to be ranked with its greatest benefactors Pasteur and Lister and in a material manner his services have been rewarded by the bestowal upon him of the Nobel Prize in Medicine. In addition, penicillin appears to be a specific for both the major venereal infections, syphilis and gonorrhoea, which it promptly *nips in the bud* so promptly in fact that the patient's defensive powers do not have the opportunity to develop an immunity. It is too early to express a long term view as to the ultimate effect of penicillin on these two diseases but the



FIG. 16. Thomas Parran

reduction in human suffering and the benefit to the offspring of syphilitic mothers are there for all to witness. In spite of all the honours he has received Fleming has remained the same modest, quiet man that he was when I first met him in Wright's laboratory in 1906. He is a member of that small and select band of scientists who possess the triple honour—the Fellowship of the Royal College of Surgeons, that of the Royal College of Physicians and the Fellowship of the Royal Society.

Thomas Parran (b. 1892). Soon after his graduation from the Georgetown University of Medicine Parran entered the Public Health Service of the U.S.A. in which he has spent most of his professional career. During 1930 to 1936 he was Health Commissioner of New York State

from 1936 to 1948 Surgeon General of the United States Public Health Service. It was while acting in this capacity that Parran was concerned with the control of the venereal diseases, the effect of which is reflected in the substantially decreased incidence of syphilis shown in Table 2 on p. 37

Parran has represented the United States Government at a number of international health conferences He was Chairman of the United States Delegation to three Pan American Sanitary Conferences was President of the International Health Conference in New York City in 1946 which drafted the constitution of the World Health Organization and he was Chairman of the United States Delegation to the first World Health Assembly In 1948 Dr Parran received the Distinguished Service Medal for his contributions to the successful prosecution of the War"

Parran s list of native and foreign honours—degrees, memberships and fellowships—are too numerous to specify but mention may be made of the fact that he received the Honorary Fellowship of the Royal Society of Medicine, is an Honorary Member of the Medical Society for the Study of Venereal Disease, and of the Royal Sanitary Institute, the Royal Institute of Public Health and Hygiene and the Society of Medical Officers of Health—all of Great Britain His work is obviously well known in this country

Immediately after Schaudinn and Hoffmann had announced their discovery of the spirochaete of syphilis, Constantin Levaditi (b 1874) began his long series of investigations and researches which, in association with a succession of collaborators and assistants, he has continued uninterruptedly (except for the two world wars) for more than 45 years. A Roumanian by birth, he studied medicine in Bucarest and in Paris, and most of his experimental work was carried out at the Pasteur Institute in Paris first as assistant to Metchnikoff and since 1926 as Professor at the Institute. He collaborated with the clinicians Queyrat Pinard and many others who furnished him with material for his clinico-pathological and scientific investigations

Already in 1905 Levaditi made several communications to the Société de Biologie on various aspects of syphilis and its causal organism agglutination of *T pallidum* in the contents of a syphilitic bulla with Manouélian he studied the distribution of the treponema in human and simian chancres and demonstrated the parasite within the blood vessels and at the meeting of the Society in October 1905 he gave details of his method of staining treponemata in sections which is still in use. In 1906 with Sauvage, he described the treponema in the ovary and even in the ova of a syphilitic infant an observation which was later confirmed by McIntosh and others. In 1906–7 with Marie he made the important observation which is referred to on p 76 that in performing the W R it was not necessary to use an extract of syphilitic liver as antigen but that an extract of healthy

tissues will answer equally well. The same year with McIntosh, he endeavoured to cultivate *T. pallidum* in celloidin sacs in the peritoneal cavity of monkeys. In this they met with scant success for the cultures were all contaminated with bacteria. With Roché, Levaditi wrote his book *La Syphilis, expérimentation, diagnostic* in 1909. Between the war years 1914–1918 experimental work was restricted, but shortly after (1919) he published a paper with Marie on treponemata from cases of general paralysis in which the opinion is strongly expressed that there is



FIG. 17 Constantin Levaditi

a neurotropic strain of the syphilitic parasite and that the neurotropic and the dermotropic should be regarded as varieties of the treponema. Then followed work on the spirochaete of the rabbit (*Sp. cuniculi*) with Marie and Nicolau, and in 1921 Levaditi began to publish his long series of papers on bismuth preparations first with Sazerac on their curative effect on animals (rabbit syphilis) then, in 1922, the confirmation of their beneficial effect on man by Fournier and Guénot led to much work being done on the mode of action of bismuth and Levaditi's suggestion that bismuth compounds have only a feeble action on spirochaetes *in vitro* unless they have been previously in contact with organ extracts particularly liver and kidney. In 1924 he wrote a book on bismuth in the treatment of syphilis,

but he continued his researches upon this subject, for in 1925 he synthesized Bistovol, a compound of bismuth and arsphenamine which was found to be active in experimental syphilis and later in human syphilis. With several collaborators he wrote papers in 1926–8 on the mode of action of bismuth preparations and the value of lipo-soluble preparations —much vaunted by the Germans—compared with insoluble preparations which Levaditi found to be far more capable of preventing syphilitic infections than the soluble ones. During this period he was engaged upon researches into the life cycle of the parasite of syphilis, of which he said the *T pallidum is only one phase.* Contemporaneous and later work included the study of the viruses of herpes and encephalitis, toxoplasmosis *and allied conditions, which culminated in his writing two further books,* one in 1935 on the Prophylaxis of Syphilis, upon which many authorities disagree with Levaditi the other in 1938 on Les ultravirus des maladies humaines. In 1946 he published work with Vaisman on the synergistic action of penicillin and bismuth in experimental and in human syphilis. Even this record does not complete the account of Levaditi's activities, but sufficient has been outlined to place him in the front rank of original investigators.

A record of epochal discoveries in connection with a single disease such as occurred in the case of syphilis between the years 1903 and 1910 is unique in medicine. Since 1910 further important discoveries have been made, but none quite so fundamental as those of 1903 to 1910 Among these later discoveries are (1) The introduction of malaria (1917) for the treatment of general paralysis by Wagner Jauregg (1857–1940). Pyretotherapy as this form of treatment is called, has since been applied to *all* forms of neurosyphilis as well as to Wassermann-fast and other types of the disease. A special apparatus—the Kettering hypertherm—has now largely replaced malaria therapy in the United States of America. (2) The value of bismuth in the treatment of syphilis as demonstrated by Levaditi and others (1921) (3) *The use of tryparsamide in neurosyphilis.* (4) The oral treatment of congenital syphilis by stovarsol (acetarsol) (5) The introduction by Hamilton in 1932 of arsenoxide (mapharsen) in the treatment of all forms of syphilis, which led to its adoption for the routine treatment of the disease by the U.S.A. and Canadian Medical Services and by the Royal Navy until the use of penicillin was inaugurated. (6) The recognition of the fact that by giving adequate treatment to all syphilitic expectant mothers the birth of a healthy infant can be practically assured. This has been hailed as one of the great discoveries of modern medicine, and in countries where its application is general congenital syphilis has been almost eradicated in the last 25 to 30 years. (7) The discovery and elaboration of the various flocculation tests (Kahn Kline, Meinicke, Sigma, etc.) have helped materially in the diagnosis and follow up of syphilitic patients (8) Most important of all the discovery of peni

cillin by Fleming and the demonstration by Mahoney Arnold and Harris in 1943 of its value in the treatment of syphilis have been followed by reports from all over the world of the curative effects of the drug in human and experimental syphilis. In spite of all these discoveries, however there are still many unsolved problems in syphilology several of which have already been touched upon in this and the preceding chapters, while others will be unfolded as the narrative proceeds.

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CHAPTER 3

INCIDENCE OF CONGENITAL SYPHILIS

IN the absence of any system of notification of syphilis it is impossible to obtain reliable figures for the incidence of the disease in adults or children. The records of the venereal diseases clinics (since 1917) give the number of new cases of acquired and congenital syphilis diagnosed each year and the total number of cases attending the clinics. In addition the returns of the Registrar General give the number of deaths certified as being due to syphilis, which (since the year 1940) have been subdivided into those resulting from (1) general paralysis, (2) tabes dorsalis, (3) aortic aneurysm (4) congenital syphilis and (5) other or unspecified forms of syphilis. The returns from the V D clinics have hitherto excluded congenital syphilis patients treated in hospitals and institutions *not working under the V D scheme* though under the National Health Service they may some day be recorded. The number of such patients treated by private practitioners will remain unspecified in the future as it has done hitherto unless perchance congenital syphilis should some day be made a compulsorily notifiable disease. In addition there undoubtedly arises every year a considerable number of cases of unrecognized syphilis acquired and congenital which may remain latent for an indefinite period. Statistics on the incidence of congenital syphilis in the pre Wassermann days were based on clinical experience alone, and after the discovery of the causal organism and the Wassermann reaction they were based on estimates calculated from certain data such as (1) the number of serologically positive children among certain classes of the population normal children, general hospital patients inmates of institutions for the blind deaf mentally and physically defective, most of these being selected groups of individuals (2) the proportion of stillbirths due to syphilis and (3) the number of positive reactors among expectant mothers. Pathological and serological investigations are likely to yield more accurate results than reliance upon history and clinical manifestations alone, but whichever method is employed unless routine serological tests are carried out on *every* patient and mother the number of congenital syphilis patients discovered will depend upon the clinical acumen of the examining physician and his index of suspicion of the disease. Unfortunately modern medical teaching appears to suggest, and at times even to state, that congenital syphilis is a rare

disease, paediatricians often holding the same view It is therefore understandable, though much to be deplored, that medical students—the practitioners of to-morrow—take little interest in the disease and hence fail to realize its importance to the coming generation and the great value to the community of the blood testing of all expectant mothers.

The incidence of congenital syphilis can be most conveniently considered under the following headings

(1) Stillbirth rates.
(2) Death rates from syphilis (*a*) in infants under 1 year (*b*) in older children and adults.
(3) Actual figures and estimates in infants and in older children and adults.
(4) Indirect evidence such as is afforded by positive serological tests in pregnancy

(1) Stillbirths

It is an age-old belief that syphilis is a common cause of miscarriages and stillbirths and particularly of repeated stillbirths in a woman's obstetric history It must not, on that account, be assumed that all stillbirths are due to syphilis, nor should one always expect to have one or more stillbirths before the birth of a syphilitic infant. Authorities give very divergent figures for these occurrences and the tendency has been with the passage of time to reduce the proportion of stillbirths which it is estimated is due to syphilis. In recent years the rhesus (Rh) factor has been shown to play a not inconsiderable part in the causation of stillbirths and neonatal deaths which formerly would have been debited to syphilis. Most authorities agree that syphilis is not a frequent cause of early abortions and that most foetal deaths from syphilis occur in the second half of pregnancy McCord (1935) is of the opinion however that syphilis is a more frequent cause of early foetal death than is now generally believed to be the case, and this opinion I am inclined to share. All are agreed, on the other hand, that syphilis in the later months of pregnancy is an important cause of premature births and stillbirths as well as of neonatal and infantile deaths up to the age of 3 months. In 1917 Sir William Osler wrote that of the 100,000 stillbirths estimated by Sir Arthur Newsholme to have occurred in this country in 1915 at least 20 000 were syphilitic, and of the 90 000 infant deaths under 1 year 15,000 to 20,000 were due to syphilis.

Bishop Harman (1917) compared the obstetric and family histories of 150 healthy and 150 syphilitic women of approximately the same social status His results are shown in Fig 18 from which several points of interest emerge. The syphilitic mothers had more pregnancies than the healthy which shows that syphilis does not reduce the fertility of mothers and the greater number of pregnancies is to be explained by the untimely

and housing had come largely into the picture, but he did not believe that improving the housing conditions of the lower strata of society would achieve the desired advance. In his view which was not shared by Professor D Baird, who opened the discussion, the deplorable figures for premature births and stillbirths and for neonatal deaths were due not solely to the conditions under which the people lived, but also to their natural weakness in breed character and/or intelligence. Doubtless there are many factors, among which I believe syphilis still holds an important place, yet this disease is not mentioned in the report of the discussion.

(2) Death rate from congenital syphilis

In his oration previously referred to, Osler said Venereal disease is and remains the despair of the statistician. Trustworthy data are not forthcoming Even in death a stigma is associated with it and the returns are everywhere but under the special caption of the disease itself Among the eleven causes of infant mortality during the first year syphilis is not mentioned." The situation has improved since Osler made these observa

TABLE I

Deaths in England and Wales under 1 year of age from Congenital Syphilis, and from to 30 years of age from Syph lis during the ears 1918 t 1949 (from the Registrar General returns)

Date	*Under 1 year*	*From 1 to 30 years*	*Date*	*Under year*	*From 1 to 30 years*
1918	1,262	241	1934	201	76
1919	1,217	184	1935	174	73
1920	1,443[1]	52	1936	162	81
921	,214	142	937	14	64
1922	874	44	938	23	70
923	797	34	939	119	68
1924	666	126	1940	00	2
1925	585	1	1941	117	11
926	586	124	942	119	107
1927	505	123	943	53	75
928	471	35	944	108	70
1929	413	124	945	106	73
1930	360	1 4	946	22	69
931	322	1 9	1947	83	43
1932	291	106	948	75	4
1933	232	102	949	61	30

Note The deaths from to 30 years of age would presumably be due to congenital syphilis (neurosyphilis or cardiovascular syph lis) in the large majority of cases.

1 The highest figures in the series.

2 The only instance of figure in col. 2 exceeding that in col.

3 The discrepancy in the deaths under year from congenital syph lis in the years 1933 to 939 inclusive given in this Table and in Table 3 is due to the revision in 1938 of the International List of Causes of Death, on which ou mortality statistics are based (re eived from strar-General Office Oct. 952).

tions in 1917 for in the following year we find in the Registrar General's returns of the deaths from syphilis that no fewer than 1,262 infants under 1 year died from the disease Table 1 gives the deaths from syphilis under 1 year of age and from 1 to 30 years of age for the period 1918–1949. The majority of individuals who die of syphilis under the age of 30 are almost certainly congenital syphilitics, the exceptions being the few fatalities among acquired syphilitics who die as the result of treatment or in rare instances from some other cause. The table is instructive, for it shows that the peak was reached in 1920 two years after the termination of the first world war and since that time the deaths fell first steeply then steadily down to the years 1939/40 During and since the second world war the numbers have fluctuated and the lowest figures hitherto recorded in this country were reached in 1949. The improvement is more marked in the deaths under one year of age than in the older age group In the former there were only 61 deaths in 1949, which represents a reduction of over 95 per cent of the 1,443 deaths recorded in the peak year 1920 the corresponding figures for the 1 to 30 years age-group were 30 in 1949 and 241 in 1918 a reduction of 87 5 per cent. Table 2 gives the death rate

TABLE 2

Death Rate from Infantile Congenital Syphilis per 1,000 related Live Births in England and Wales and in the U S.A. from 1933

	1933	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
England and Wales	0·33	·30	·26	·24	·19	·16	[illegible]	[illegible]		[illegible]	·23	[illegible]	[illegible]	[illegible]	·09	[illegible]	[illegible]	·04
U. S. A. White	·44	·41	·4	·41	·37	·33	[illegible]	·35	[illegible]	[illegible]	·16	·13		·07	[illegible]	[illegible]	[illegible]	[illegible]
U. S. A. Non-White	[illegible]	·84	·77	1·07	[illegible]	·81	·60	·52	[illegible]	[illegible]	[illegible]	·33	[illegible]	[illegible]	[illegible]	·63	·44	[illegible]
U. S. A. Total	[illegible]	·74	·70	·74	[illegible]	0·63	·67	[illegible]	·4	[illegible]	[illegible]	·27	[illegible]	[illegible]	·14	[illegible]	[illegible]	[illegible]

The figures for England and Wales are from the Registrar-General's returns. Those for the U.S.A. are kindly supplied by the Medical Director of the Venereal Disease Division of the Public Health Service, Washington, D C.

The English death rate per 1,000 live births has improved from ·33 to ·04 in 18 years (that is, by nearly 90 %), whereas the American rate has improved from ·44 to ·05 in whites in 17 years (that is, by rather more than 90 %), and from [illegible] to ·44 in non-whites in [illegible] years (that is, by approximately [illegible] %).

under 1 year of age from congenital syphilis in England and Wales and in the United States per 1 000 related live births. It is seen that the English rate was more than halved between the years 1933 and 1940 then rose by almost 50 per cent in 1943 since when there has been a very considerable fall. A similar reduction in the mortality rates is shown by the American figures, but here the decline has been almost uniformly progressive without any setbacks due to the war This indicates a mitigation in the severity of the infection in infants and reflects also the beneficial effects of modern methods of prevention and treatment, but the total incidence and mortality from congenital syphilis are still considerably greater than they should be or need be (see later p 39) It has been shown in several countries that when adequate antenatal supervision and

treatment have been carried out congenital syphilis has been rendered practically non-existent.

In order to demonstrate that congenital syphilis in infancy was not the rare disease it was so often stated to be, the figures for deaths under 1 year of age from congenital syphilis, meningococcal meningitis and tuberculosis of the central nervous system for the years 1933–1949 have been taken from the Registrar General's returns and are presented in Table 3

TABLE 3

Deaths under 1 year of age from Congenital Syphilis, Meningococcal Meningitis and from Tuberculous Meningitis and Tubercle of the Central Nervous System (from the Registrar-General's returns)

Disease	1933	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49
Congenital syphilis	207	179	35	146	[illegible]	13	67	[illegible]	17	[illegible]	153	[illegible]	[illegible]	122	83	73	[illegible]
Meningococcal meningitis	3	170	[illegible]	180	99	73	[illegible]	4 1	3	[illegible]	187	59	[illegible]	42	82	98	
Tuberculous meningitis and tuberc. of C N S.	234	232	56	97	223		164	199	[illegible]	[illegible]	179	64	[illegible]	49	53	1 3	85

See Note to Table

It shows that the deaths from congenital syphilis are by no means insignificant, and as from my own observations I am convinced that both the incidence of and the mortality from the disease are greater than the official figures would lead us to believe, it is quite possible that in the year 1943 for example, when 153 infants are stated to have died from congenital syphilis against 187 from meningococcal and 179 from tuberculous meningitis, the deaths from congenital syphilis may have equalled or even exceeded those from either of the other two diseases named.

(3) Incidence of congenital syphilis in infants and in older children and adults

As was stated at the beginning of this chapter it is impossible to produce actual figures for the incidence of the disease and the estimates which have appeared in the literature differ so widely from one another as to be practically valueless. An important point to bear in mind is the fact that since the mortality from congenital syphilis is much greater in infants under 1 year than it is in older children, the incidence of the disease will be correspondingly higher the younger the age-groups studied

Table 4 shows the alleged incidence of congenital syphilis under 1 year and at all ages in Great Britain compiled from the V D clinic returns since the year 1931 It does not, however disclose all the facts, for as has been previously stated, the clinic returns have not hitherto included (1) patients attending hospitals and other institutions which are not working under the V D treatment scheme and (2) cases diagnosed and treated by private

practitioners. Furthermore, there will always be a number of undiagnosed cases with overt symptoms or which may be latent.

TABLE 4

Recorded (V D Clinic) Incidence of Congenital Syphilis in Great Britain from 1931 to 1951

Year	*England and Wales*			*Scotland*		
	Number of new clinic cases of Cong Syphilis		*Case rate under 1 year per 1,000 births*	*Number of new clinic cases of Cong Syphilis*		*Case rate under 1 year per 1,000 births*
	All ages	*Under 1 year*		*All ages*	*Under 1 year*	
1931	2,439	339	0·53	710	180	1·95
1932	2,144	302	0·49	657	173	1·90
1933	2,0 6	305	0·53	641	64	1 89
1934	2,008	296	0 49	658	61	1 81
1935	2,031	251	0·41	540	38	1 56
1936	1 908	241	0·39	540	138	1 55
1937	1,819	211	0 34	575	136	1 54
1938	738	2 6	0·34	681	174	1·96
1939	1,614	217	0·35	497	134	1 54
1940	1,358	9	0·3	358	00	1 15
1941	1,380	223	0·37	352	92	·02
1942[1]	1,464	245	0·37	319	85	0·93
1943	1 727	31	0 45	379	142	1 49
1944	1 552	345	0·46	416	174	8
1945	1,355	316	0 47	30	148	1·70
1946	1 382	363	0·44	363	170	1 62
1947	1,353	343	0 38	358	169	1·67
1948	,407	372	0 48	337	197	96
1949	,4 7	353	0·486	294	164	·77
1950	1 223	227	0 33	242	130	40
1951	127	156	0 23	166	78	0·86
1952	949	110	0 163	178	87	0 41

[1] The figures down to 1942 are from Dr Wattie' paper those for the subsequent years have been supplied by Dr Wattie Dr McElligott of the Ministry of Health, and Dr Ian Sutherland, Department of Health for Scotland. Dr Wattie s notes to her original Table are as follow This table is compiled from the recorded clinic returns. The marked difference in the rates for the two countries shows that the clinic figures cannot be taken as an accurate index of the incidence. In addition, it is probable that the special returns under the Glasgow scheme weight the Scottish incidence as compared with the English Although a decrease has taken place the incidence is still unduly high.

In a paper written in the year 1943 I said that whatever the actual incidence of congenital syphilis may be, there is no doubt that, with the decline in the incidence of adult syphilis since the first world war down to the year 1940 the incidence of congenital syphilis had also fallen (see Tables 1–3). During the 6-year period 1917–1922, I saw at the clinic of the Hospital for Sick Children, Great Ormond Street, 322 new cases of the congenital disease, a yearly average of 53 cases, whereas during the six years 1933–1938 I saw only 123 new cases at the same clinic, but an additional 73 cases from the London County Council hospitals and the London School for the Blind, yielding a total of 196 cases a yearly average of 32.

These figures show a considerable decline in the incidence of the disease but the fall is not nearly so great as that shown in the deaths from congenital syphilis in Table 1 With the increase in the volume of adult syphilis which inevitably accompanied the second world war there was a correspondingly sharp increase in the incidence of the congenital disease, mainly in children under 1 year (see Tables 2 and 4) but the latest figures show a gratifying reduction in the incidence of children under 1 year

As regards the incidence of congenital syphilis in older children and in adults, my experience leads to the belief that this is underestimated even more than in the infantile form of the disease. Several factors contribute to this unfortunate state of affairs. Firstly the disease may be latent, that is to say the stigmata may be absent even though the serological reaction, if tested would be found positive but unless the possibility of congenital syphilis is borne in mind, in the absence of stigmata a blood test is usually omitted Secondly in older congenital syphilitics the serological reaction often diminishes in intensity—according to Dean (1912) this happens *rapidly after the 16th year in many cases—and it may eventually become* negative, so that patients with mental deficiency eye trouble deafness, cardiovascular disease and so forth may give negative serological reactions and in consequence be regarded as non-syphilitic. The elect know that this view is erroneous, but it has still to become appreciated by the many This aspect of late and adult congenital syphilis will be further considered when the relation of the disease to mental deficiency is discussed (see Chapter 8) Thirdly stigmata such as nodes on the tibiae, Hutchinsonian teeth, scars on the corneae and so forth may gradually fade and disappear as the patients advance in years and with a doubtful or negative blood test the syphilitic nature of such a case may be overlooked Many authorities have recorded such cases and I have come across several myself The following case-history illustrates how easily a syphilitic family may pass unrecognized for years and hence results in very fallacious statistics of the incidence of the congenital disease

Horace P at the age of 3 years, was brought to the Outpatients Department of the Hospital for Sick Children, where he was seen by my former colleague, Dr W G Wyllie in July 1928 He was backward, unable to walk, talked very little was dirty in his habits and dribbled at times. He was born at full term, weighed 7 pounds and is said to have had no infantile symptoms of syphilis. On examination he had the appearance of a mentally-defective child, the fontanelle being still open there were no abnormal physical signs to be detected in the chest or abdomen except that the ribs showed a well marked Harrison sulcus. The lower ends of the radius and ulna were enlarged. His weight was only 20½ pounds. The serological reactions of mother and child were tested *the mother gave a weakly positive W R and a positive Kahn the child a doubtful W R and Kahn test* The family history was as follows

Father Born 1887 gave no history of venereal disease and had not been in the Army W R. 1928 negative.

Mother Born 1891 no history of any rash or sores. Her mother died in childbirth at 43 after having had 17 children of whom 11 survived. Her father died aged 79. She was married 1910.

Children

1 F 1910. Died at 8 months of fits.
2. 1911 S.B
3 1912. S.B
4. M. 1913 Partially blind since birth. History given later
5 F 1915 Died at 8½ years of peritonitis.
6 M. 1916 Premature birth died at 14 days.
7 M 1917 Flattened bridge of nose. *W.R. 1928 negative K positive.*
8. 1919 Twins (*a*) S.B., (*b*) alive and well. *1928 W.R. and K. not quite a clear negative* At 18 years of age he was said to be "well and strong
10 M. 1921 *1928 W.R. and Kahn were not quite a clear negative* At 16 years of age he was an errand boy and apparently well.
11 M 1923 *The blood tests were not quite clear* (*1928*). At 14 years he was still at school and well
12. M 1925 The patient. No infantile syphilitic history Backward and dirty in habits at 3 years. *W.R. and K. doubtful.* Negative after two courses of injections (sulpharsphenamine). Cerebrospinal fluid negative.
13 F 1927 W.R negative at 1 year
14. M. 1930. Said to have leg trouble, but patient not brought for examination.

At the time we first encountered the family at Great Ormond Street in 1928, although we suspected syphilis and actually treated child 12 with antisyphilitic drugs, we could not satisfy ourselves there was actually syphilis in the family The treated child did not show a great deal of improvement, which may have been due to the fact that his serological reactions were not positive and that he was, therefore, not actually infected, but that the symptoms were possibly due to germinal or developmental defects consequent upon the mother's syphilis. In 1937 in following up the family and after a great deal of persuasion, children 12 and 13 were seen again. The boy was very small, was going to school and although the mother said he was not backward he had a heavy dull look. The sister (No. 13) was also small but well. Both children now had negative serological reactions.

At this time information was obtained about the eldest living child, No 4 in the list, which enabled us to establish the syphilitic basis underlying the tragedies in this family's history He is said to have been partially blind since birth. At the age of 17½ years a report from the Eye Hospital stated "vis. R. 6/60 L. 1/60 not improved with glasses. Gross fundus disease in each eye. Three months later he was admitted to an institution for the blind with the diagnosis of "retino-choroiditis and nystagmus." *No blood test appears to have been taken of the patient or of any members of the family* When the mother informed me where the youth was, I wrote to the medical superintendent, and on being told what the ophthalmic surgeon had diagnosed, wrote again asking that the blood and spinal fluid might be sent to me for investigation, and suggesting the possibility of syphilis. There was no reply to this letter but it apparently roused the medical superintendent to activity for although the patient had already been in the institution for 6 years with the initial diagnosis of retino-choroiditis, which was reiterated in a clinical note 4 years later by the ophthalmic surgeon to the institution, nothing active had been done until after the receipt of my

letter The patient was then sent to a London hospital for a report on the condition of the central nervous system. The report stated that there had been a history of an epileptic fit, but since admission the patient had had no further fits and no physical signs could be found in his nervous system, except a raised protein content (said to be 0·28 %) and a straw colour of the cerebrospinal fluid sugar present, globulin increased and the W R. negative. There was marked choroido-retinitis, and the pupils, though circular and equal and reacting to light, did not react to accommodation. The serological reaction of the blood was not tested which seems a strange omission in view of the presence of the choroido-retinitis and of the family and personal history The patient continued with the symptomatic treatment ordered (pot. bromide and liq arsenicalis) and 4 years later (1944) I was informed that he had become "mental. There were 13 pregnancies (with 14 children) in this family most of whom were almost certainly syphilitic, yet they eluded any inclusion in a syphilitic category until one was able to obtain the facts over a period of 14 years.

This one history alone suffices to show how difficult it is to give any reliable estimate of the incidence of congenital syphilis after the first few years of life. The literature contains many such estimates, from which the following may be quoted. In 1930 Marjorie Smith-Wilson, then Medical Secretary to the British Social Hygiene Council estimated that the number of affected children of school age attending the elementary schools in England at any one time lay somewhere between 7 000 and 20 000 and she remarked that even the lower figure was sufficient to make one realize that the incidence of congenital syphilis was of very real importance. Kettlewell of Plymouth wrote in 1923 that a rough examination of 1 000 children in four schools showed that 8 per cent exhibited physical signs of the disease. By way of comment one would add that in addition to the alleged *8 per cent of the scholars who exhibited signs of the disease* there would be at least another 4 per cent of latent cases children with positive blood tests only Against this estimate should be quoted the findings of Grumach, who in a new survey of venereal disease among children carried out in Berlin in 1929 found only 0 125 per cent among 88 298 children. And finally Leredde writing in 1923 says If it is true that heredo-syphilis kills 40 000 children every year and this figure appears probable from the investigations of Couvelaire upon the number of syphilitic stillbirths, we must conclude from the figures given by Bishop Harman Leredde and Drouet that about 150 000 congenitally syphilitic children are born in France every year and that there are several million congenital syphilitics living in this country today! He adds that the condition is undiagnosed or unsuspected in more than 95 per cent of the cases. The situation in the United States down to the year 1938 is well summarized by Whipple and Dunham in their review (*loc cit.*, p. 388). They state that The incidence of congenital syphilis in children is even more difficult to determine than that in adults Because of a general lack of morbidity statistics concerning the disease, data for the whole country

are not obtainable and surveys of isolated groups vary markedly with the composition of the groups studied. From a compilation of reports in the literature made by the U.S. Public Health Service (1936) the incidence of congenital syphilis among all children has been estimated at 2 per cent when these data were restricted to infants only the rate was 5·6 per cent Among white children the rate is estimated to be 1·7 per cent, but among non-white children 12·2 per cent. When the data were considered in relation to economic status, it was found that the incidence of congenital syphilis among white children in clinics was 5·3 whereas among children of the well to-do it was less than 1 per cent. From the one-day census the Public Health Service[1] estimated that of the 683,000 individuals with syphilis constantly under observation and treatment in the United States, at least 60,000 were suffering from an infection transmitted from the parents.

Jeans and Cooke estimated that 2 8 per cent of all the babies born in St. Louis were syphilitic and that although the coloured race formed only 9 per cent of the city s population, it furnished almost one half of the cases of infantile syphilis. For one year (1938/9) Clifton and Heinz examined all the new patients, aged from one day to 13 years, 5 625 in number attending the Children s Memorial Hospital in Chicago Of these 27 were found to be syphilitic, 26 congenitally (0·46 per cent) and one acquired by transfusion and the authors state that 22 of the 27 cases were diagnosed clinically and before the result of the blood test was known.

In September 1949, Dr Theodore Bauer Chief of the United States Public Health Service, drew attention to the fact that although the incidence of syphilis in the U S.A. was probably on the decline, the number of cases reported as congenital syphilis had remained at a constant level for the past 5½ years. This despite the fact that so many pregnant women were treated with penicillin, which the Americans regard as being the most effective treatment for syphilis in pregnancy In Tables 2 and 3 we saw that the mortality rate from syphilis had markedly diminished in the U S.A. and in Great Britain during the last 10 to 15 years. Why then asks Bauer had the morbidity rate not similarly declined? It may be that the improvement in case finding has neutralized a possible decrease in incidence we do not know he says, but of one thing we may be sure there is too much congenital syphilis and too much of it goes untreated into the later years of life.

From the foregoing widely divergent estimates it is obvious how impossible it is to come to a definite conclusion as to the actual prevalence of congenital syphilis. The precise numbers could only be ascertained by making a careful physical examination and a serological blood test of

[1] U S. Public Health Service (1937) *Proceedings of Conference on V. D. Control Work*, Dec 1936 Supp No 3 to V.D I Washington

infants from 3 to 6 months of age.[1] Even this would fail to disclose the number of syphilitic miscarriages stillbirths and neonatal and early infantile deaths unless adequate pathological and autopsy investigations were carried out on these cases and the mothers histories carefully inquired into

In a large series of families the number of latent cases has been found to vary from 25 per cent (Dennie and Pakula, *op cit* p 420) to 36 per cent (Jeans and Cooke *op cit* p 211). From my own investigations it would be a conservative estimate if for each family in which a syphilitic child is discovered one added one syphilitic stillbirth or one latent case With the advent of penicillin therapy and antenatal prophylaxis, the future prospects are more promising

(4) Indirect evidence syphilis in pregnancy

At this stage we shall consider only the numerical aspect, reserving for subsequent discussion the pathological bacteriological and other data in relation to pregnancy and syphilis. Most authorities are now convinced that the parasite of syphilis is conveyed transplacentally from mother to foetus, so that the number of expectant mothers who harbour the treponema, and are in consequence potentially infective to their offspring, is of medical and socio-economic interest and importance Not every syphilitic mother will of necessity give birth to an infected child, nor do we know the conditions which convert the potentiality into an actuality These are among the unsolved problems of syphilology

In the absence of primary or secondary lesions the taking of a serological test is the easiest way to diagnose syphilis in an expectant mother and where this has been done on a large scale it has been found that the incidence of positive reactors varies greatly in different localities from as low as 1 per cent or even less in some cities in this country the United States and in parts of Europe, to 10 or more per cent in less enlightened and more heavily infected areas In 1922 Cruickshank, from observations made at the Royal Maternity and Women s Hospitals in Glasgow found that in a series of 1900 unselected patients, over 9 per cent gave a positive W R. from which he concluded that nearly 10 per cent of the women of the hospital class in Glasgow were or had been syphilitic. He found that of 1 350 infants born in Glasgow the placental blood was positive in 4 5 per cent. Yet when the positive reactors were re-examined, from 3 weeks to 20 months later the reaction was clearly negative in the great majority of cases from which he concluded that the incidence of congenital syphilis in the population was considerably over-estimated.

In 1930 Harrison estimated that of the 700 000 women who became

[1] Under the age of 3 month the serological reaction may not yield reliable results (see p 81)

pregnant every year no fewer than 16 000 (2–3 per cent) and probably many more, should be under treatment for syphilis throughout their pregnancies, but nothing approaching that number are treated at the Centres, thereby leaving a large hole in the net of the venereal diseases prevention scheme. And on a previous occasion when opening a discussion on the antenatal treatment of syphilis, Harrison (1928) said "We for our part can only present those who could carry out the necessary treatment, namely the patients' medical advisers, with the facts, leaving it to their consciences to decide if they will or will not do anything to prevent what the lowest estimates such as I have given you show to be a terribly large evil." Fortunately for the well-being of the rising generation there has been a steady decline in the morbidity and mortality from congenital syphilis (see Tables 1–4), which it is to be hoped will manifest an ever increasing pace until the disease shall have become practically a relic of the past.

The City of Glasgow offers a striking example of the valuable results obtained by the co-operation of the City's Venereal Diseases, Antenatal and Child Welfare Schemes. Nora Wattie (1944) records that when the Glasgow antenatal clinics were established in the year 1924 less than a thousand women attended during the first year and about 5 per cent of them showed positive serological reactions (see Table 5). The attendances increased steadily year by year and as a result the amount of infection in the mother and infants has as steadily declined, so that in the year before the second world war (1938) 8,400 samples of maternal blood were tested, of which 1·7 per cent were positive, and the number of cases of congenital syphilis under 1 year of age was 53, from having been 202 in the year 1924. The record low level of early congenital syphilis was reached in 1941, when only 15 cases were diagnosed and the positive reactors among the 8 300 mothers tested numbered only 0·8 per cent. Since then there has been an increase in all the figures—for example, in 1947 the number of congenital syphilitics under 1 year was 25, and of the 13 250 maternal bloods tested 1·46 per cent were positive, due largely to war conditions and the aftermath of the war. Wattie noted that during the war years there was increased promiscuity among married as well as unmarried women, who often became infected *after* having already been found to be W.R. negative earlier in their pregnancy. The latest figures for Glasgow show that in the years 1950–1951 the low records of 11 and 6 respectively were obtained for cases of congenital syphilis under 1 year of age. The success achieved by these joint schemes was due in great measure to the enthusiasm of those working them and also to the fact that the women received their treatment, both before and after the birth of their babies, *at the place where they first attended*, either the antenatal clinic or the maternity hospital or the child welfare centre.[1]

[1] By this procedure the mother is spared the inconvenience of making journeys to two clinics should she already have one or more children attending the child

TABLE 5

City of Glasgow Figures for Congenital Syphilis, showing the Improvement effected by the Corporation's Scheme for Venereal Diseases Clinic, Antenatal and Child Welfare Schemes

Year	*Cases of Congenital Syphilis*		*No. of antenatal specimens examined*	*Per cent positive*
	Under 1 year	*At all ages*		
1924	202	662	Less than 1,000	About 5
1925	211	575		
1926	174	493		
1927	119	551		
1928	113	498		
1929	154	351		
1930	128[1]	260		
1931	73	270		
1932	72	240		
1933	67	261		
1934	65	302		
1935	53	228		
1936	60	218		
1937	36	177	7,855	1·8
1938	53	141	8,102	1·7
1939	39	136	8,616	1·2
1940	23	96	8,714	1·3
1941	5	67	8,327	0·8
1942	27	71	10,265	1·18
1943	32	97	11,067	1·7
1944	29	83	10,260	1·3
1945	32	72	10,853	1·8
1946	27	72	13,946	1·23
1947	25	80	13,250	1·46
1948	28	60	12,692	0·96
1949	22	52	10,497	0·83
1950	1	39	10,692	0·70
1951	6	24	9,796	0·65

[1] The average annual births in Glasgow number 22,000. In 1930 the attendances at the Clinic were just over 3,000. In 1931 they were just over 6,000, hence the big drop in the number of congenital syphilis cases under 1 year reported in 1931

The number of positive reactors among expectant mothers varies within wide limits, not only from one country to another and from one city to another in the same country but even at different places and times in the same city In 1943 when collecting data for a paper upon the prevention of congenital syphilis I sent out questionnaires to 31 representative authorities in Great Britain and in only 11 districts were routine blood tests carried out on expectant mothers. Probably the fact that the war was still on accounted for the small proportion of positive replies. The situation at the present time has considerably improved but the disturbing factor

welfare centre It was my practice for many years at the Children's Hospital Great Ormond Street, to treat both mother and child at the Special Clinic. An expectant mother should not be referred to a Venereal Diseases Clinic for treatment but to one designated for Women's Ailments or one bearing a non committal name

which may still be operative, was that the number of positive reactors varied *between 0·27 per cent and 2·79 per cent* during the previous 9 or 10 years. These figures were furnished by two laboratories under one controlling authority the status of the patients being almost similar in the two parts of the city served by the antenatal clinics. The higher figure is more than ten times as great as the lower figure, which indicates a lamentable lack of reliability in the performance and results of the Wassermann test as carried out by some laboratories.

From the most reliable results an estimate of between 1 and 2 per cent would appear to be justifiable, and as was found to be the case in Glasgow the rate had gone up in 1941 and 1942 In the autumn of 1943 a large-scale investigation was instituted in the Tyneside district of England one item of which included the routine antenatal testing of expectant mothers. Of 4,425 women tested in a 4 month period, 57 or 1·29 per cent were positive Price reports, however that of 6,809 expectant mothers tested by him in London during the 3 years 1949–1951 only 44 (0·649 per cent) had positive serum tests. Of the position in the U.S.A Dr J R. Heller of the Public Health Service wrote in 1943 (personal communication) Data on the proportion of positive tests in the different States are somewhat incomplete at present. From 1935 to 1940 1·69 per cent of 282 600 expectant mothers showed evidence of syphilis. In Connecticut in 1942 0·75 per cent of 27 500 were positive or doubtful in Michigan 1939–1940 1 per cent of 20,400 in California 1940–1941 1·6 per cent positive in 156,000 tests carried out.

In Melbourne, Australia, Jago (1930) found 4 per cent positive among 1,012 expectant mothers, whereas 6 4 per cent positive reactors were found among 3 040 consecutive patients of the Queen Victoria and Women s Hospitals, Melbourne. In Batavia, Java, Loe Ping Kian (1941) found that about 7 5 per cent of the Chinese and 6·1 per cent of the Indonesian pregnant women gave positive blood reactions during the years 1931–1937

As previously said, all positively reacting mothers will not necessarily give birth to syphilitic infants, for the likelihood of their doing so will diminish with the age of the infection in the mother Nevertheless one has not infrequently seen a syphilitic babe born to a mother whose infection was 10 or more years old and who had already borne several healthy children. Other observers have recorded similar experiences. It follows, therefore, that the number of syphilitic offspring—miscarriages, stillbirths and living children—will not correspond to the number of positively reacting syphilitic mothers, but what the proportion may be cannot be stated with any degree of certainty On the other hand, numerous instances have been reported of mothers who were known to be syphilitic, yet at the time of the antenatal blood test were serologically negative, giving birth to infected infants If we accept the estimate of 1 to 2 per cent as the probable number infected among the 700,000 women who become

pregnant in this country each year it follows that 7 000 to 14,000 women needed antenatal treatment to safeguard their offspring and as nothing approaching this number of expectant mothers are treated annually in this country several thousands—it may be two three or more thousands—of syphilitic foetuses and children may be born each year In the Scandinavian countries, where antenatal testing and treatment have long been practised congenital syphilis has been almost eliminated, and we have seen how in Glasgow by energetic action and enthusiasm on the part of civic authorities, the reported annual incidence was reduced from 202 in the year 1924 to 6 in 1951 a period of less than 30 years. If similar energy and enthusiasm could be aroused throughout the kingdom thousands more healthy children would be born and reared each year many mothers would not have to go through their pregnancy only to be robbed of its fruit at the termination thereof or shortly after and our institutions for the blind, the deaf the halt and the lame as well as many of our mental hospitals would be bereft of a considerable proportion of their population During the course of 25 years congenital syphilis would then indeed become a rare disease, which many members of our profession, in my experience erroneously maintained that it was down to the outbreak of the second world war

Osler in his oration on the Anti Venereal Campaign (1917) said The syphilis we see but do not recognize everywhere awaits diagnosis so protean are its manifestations. Paradoxically one of its protean manifestations is its capacity to remain latent the congenital variety perhaps even more so than the acquired and this latency of congenital syphilis has, I believe become more frequent since the first world war From about the year 1936 onwards one saw at the clinic at Great Ormond Street mothers of congenitally syphilitic infants who were themselves congenital syphilitics (facies suggestive teeth), yet had never been recognized as such and hence had received no treatment for the disease. During the second world war one came across several cases of unrecognized congenital syphilis among soldiers whose fathers had served in the 1914–1918 war This latency of the congenital disease may possibly be accounted for in this way The father having contracted syphilis, was given 6 or 12 injections of arsphenamine and a heavy metal which at that time was regarded as adequate treatment or as much as the exigencies of the Services would allow This in many cases rendered the patient non infective for a time and a child procreated under such conditions might subsequently be born healthy and escape the infection If however a longer time had elapsed since the termination of the father's treatment some of the treponemes which had been incapacitated but not actually killed off by the treatment and had perhaps assumed some other form—possibly ultra microscopic—might if transferred to the mother in this condition have given rise to a very mild infection in the child so mild in fact that it could

and did remain latent for years. Such a sequence of events is not so likely to recur after the second world war since the arsenobenzene heavy metal treatment of the disease was then so much more thorough than it was 25 or 30 years previously. If however reliance comes to be placed on penicillin alone or even upon penicillin and arsenic, and treatment is discontinued after a few weeks or months, the same state of affairs may arise as did after the 1914–1918 war with the result that many cases of unrecognized congenital syphilis may occur in the future. All authorities are agreed that florid cases of congenital syphilis are much less common today than they were 25 years ago and that nowadays the diagnosis of the disease is much more difficult than it was formerly. This is probably in part due to a diminution in virulence of the treponema consequent upon the treatment the parents may have received or to an acquired racial immunity.

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CHAPTER 4

TRANSMISSION

In Chapter 2 it was stated that the early writers on congenital syphilis thought the infection was conveyed to the offspring during parturition or possibly by the mother's milk. When Paracelsus recognized the disease in a newly born infant, it was obvious that infection could occur *in utero* Ferrier (1553), it will be remembered stated that the virus could be attached to the male or female germ-cell and also that post-conceptional transmission of the disease occurred and during the succeeding 300 years little progress was made towards the elucidation of the problem of the transmission of syphilis from parent to offspring Most authorities believed in the paternal origin of congenital syphilis, which is quite understandable seeing that so many mothers of these children show no objective signs of disease. This view prevailed right into the present century based as it necessarily was until that time, upon clinical and anamnestic grounds. With the discovery of the parasite of syphilis and of the Wassermann reaction, two important aids to a clearer understanding of this much debated problem were placed in our hands In consequence, during the past 40 years the theory of paternal transmission, which was almost exclusively held by syphilologists of the nineteenth and early twentieth centuries, has been replaced by the view that transmission is from the mother and that it is nearly always transplacental. However there are still a few diehards and in 1946 Golay of Geneva made an interesting contribution to the subject in which he maintained that paternal congenital syphilis and its corollary conceptional syphilis were possible and even probable and that the acquisitions to our knowledge referred to above in no way conflicted with the views of the classical authorities on paternal transmission.

Golay asks What are the theoretically possible modes of infection in congenital syphilis? and his answers are as follows

(1) Paternal transmission or infection of the ovum by the seminal fluid at the time of fertilization.

(2) Maternal germ transmission of ovular congenital syphilis (Golay) due to pre-conceptional infection of the ovum.

(3) Infection of the fertilized ovum or foetus by the mother—maternal

transmission, the mother having acquired her infection in one of several ways

(a) before or after marriage and without pregnancy resulting
(b) at the time of conception and
(c) during pregnancy that is, post-conceptional syphilis.

(4) Pre-parturitional transmission from mother to foetus.
(5) Parturitional infections.
(6) Infection via the mother's milk.

Several of these paths of infection would give rise to a form of *so-called* congenital syphilis more nearly allied to an acquired neonatal syphilis, similar to that which an infant might contract from an infected wet nurse or other source. (See Chapter 13.)

It seems likely that the varied types of congenital syphilis met in practice depend (1) upon the different modes of transmission, particularly (3), (4) and (5) above, and the dates of the crossing of the placental barrier by the treponema (2) upon the age of infection in the father and (3) upon the amount of treatment the parents, especially the father had received. A mother adequately treated during pregnancy should give birth to a healthy infant but varying degrees of mitigation of the infection may result from her inadequate treatment.

It is of importance to emphasize two facts which are the outcome of modern practice that infantile congenital syphilis is now (1) more difficult to diagnose and (2) more likely to be rendered latent or unrecognized than was formerly the case. This imposes upon paediatricians and general practitioners the obligation ever to bear in mind the possibility of a latent or mute form of the disease.

Let us consider these various possibilities in greater detail.

(1) Paternal transmission

The nineteenth-century syphilologists practically all believed in this mode of transmission and as the mothers not infrequently showed signs of syphilis *after* the birth of their infected infants, whereas they appeared perfectly well before pregnancy it was presumed that the mothers had become secondarily infected by the foetus *in utero* transplacentally. The process by which this was supposed to occur was called by Ricord choc en retour. Jonathan Hutchinson strongly supported the doctrine of paternal transmission, of which he wrote that evidence on this point seems to me overwhelming

A case[1] which occurred in my own experience seemed to support this view. It was that of a congenitally-syphilitic father whose first child died of "marasmus" at 2 months the second child had symptoms of congenital syphilis-rash,

[1] This case is also referred to in Chapter 9 "Third-Generation Syphilis

marasmus and convulsions at 5 weeks and a positive Wassermann reaction The mother's W R. was negative on several occasions, even after a provocative injection, and during the 17 years that she was under observation she never showed any sign of syphilis and had four subsequent pregnancies. The first of these, the third child, had no symptoms of congenital syphilis but had a large bossed head had two negative blood tests at 2 and 7 months of age, and died of "bronchopneumonia" at 10 months. The next child died in 2 days of "congenital heart. The last two children showed no signs or symptoms of syphilis up to the age of 11 and 7 years respectively and had several negative blood tests. The father had been given a considerable amount of treatment which resulted in his Wassermann reaction becoming negative after about 6 years, just before the birth of the last two children. It may be contended that the mother had latent syphilis, even in the absence of signs or symptoms of the disease (except for the begetting of syphilitic children) and with persistently negative serological tests for 17 years Unfortunately contact with the family was lost during the second world war

One has come across a few cases in which the mothers of babies with symptoms of congenital syphilis and positive serological tests have given no history of syphilis and have manifested no signs or symptoms of the disease, including negative blood tests. Others have recorded similar experiences and the usual explanation is that the mothers have latent syphilis Such cases, admittedly rare though they be, seem to me to support the possibility of paternal infection, though it is difficult to explain why the mother fails to show any of the usual signs or symptoms of the disease Possibly if they could be followed to their logical conclusion and searching investigation carried out post mortem, pathological or parasitological evidence of infection might be forthcoming

(2) Maternal germ transmission

The shifting of the emphasis from paternal to maternal transmission does not solve *all* our problems It is possible for the first infected child to be an instance of paternal transmission, and that the mother is infected by that child (' choc en retour ') Subsequent children would be the offspring of two syphilitic parents, but would doubtless be examples of maternal transmission, for such a mother can give birth to a syphilitic child by a healthy father It has already been mentioned and it is not uncommon to find, that a mother with a positive blood test may bear healthy children in some cases even alternating with syphilitic ones We saw several families in which such sequences took place.

Some of the earlier investigators (Levaditi and his collaborators McIntosh, Manouélian, Sauvage and Hoffmann and Wolters) observed and depicted the parasite within the Graafian follicle and actually in the ovum itself This suggested a possibility of transmission of syphilis which has, I think been too lightly brushed aside. McIntosh wrote in 1909 After the demonstration of the treponema inside the ovum of the congenital infant it does not require great imagination to conceive a similar

occurrence in an adult syphilized woman The usual objection raised to the possibility of an hereditary infection in the case of a woman with acquired syphilis or the victim of congenital syphilis is that such an infection must lead to the destruction of the ovum. Infection of the ovum does *not* necessarily lead to its destruction. Although, as McIntosh said, infection of the ovum may not lead to its destruction, it may possibly result in faulty development. There are several instances in nature where a parasitic micro-organism is hereditarily transmitted via the ovum, such as in the case of pébrine, the disease of the silkworm moth. The micro-sporidium may infect the ova of the moth, giving rise to infected caterpillars which are smaller and weaker than normal. Similarly in piroplasmosis of cattle and dogs, infection is conveyed from the female tick to the offspring (larvae) through the ovum also spirochaetes (*Sp recurrentis*) infect the ova of the tick vector *Ornithodorus* the resulting larvae being also infective. In the case of hereditary infection in ticks, the parasites do not seem to have any deleterious effect on the offspring [1] There appears to be no biological reason therefore, why an ovum infected with *T pallidum* could not develop normally and give rise to an hereditary form of congenital syphilis, such as syphilis of the third generation (see Chapter 9) or develop abnormally as do the caterpillars of the pébrine-infected moth mentioned above, and so give rise to various forms of congenital malformation. It is possible, too that the genes of the germ cells may be so affected by a resting or attenuated form of the parasite (or by an alleged syphilotoxin) that a true hereditary effect upon the offspring may result. This might take the form of a liability to certain diseases, especially early malignant disease, if an independent life be reached, or a liability to malformations or monstrosities and congenital defects. All this is envisaged in the important work of Warthin, especially in his 1916 article and his Hunterian Lecture (1918)

Levaditi with Schoen and Sanchis Bayarri, Meirowsky and others described developmental, evolutionary or multiplication forms of the parasite which were often unrecognizable as being allied in any way to treponemata, and these forms have recently received confirmation from DeLamater and his associates. Typical treponemata have only rarely been found in the foetus before the fifth month of gestation but it is possible that atypical or developmental forms may occur much earlier

(3) Maternal transmission of the infection to the fertilized ovum or foetus

This mode of transmission is undoubtedly the commonest and that which has most adherents at the present day It postulates the existing infection

[1] I am indebted to Dr C. A. Hoare, F.R.S., of the Wellcome Laboratories of Tropical Medicine for bringing to my notice these instances of hereditary transmission of infection

of the mother which, as was stated above, may have been acquired in one of several ways

(*a*) She may have become infected before or after marriage by her husband or other partner but without pregnancy supervening In such event she would almost certainly show signs of syphilis, probably a primary lesion—which if present in the cervix uteri might easily be overlooked—and almost certainly the usual secondary manifestations Failing treatment, a syphilitic foetus or infant will in the majority of such cases result from a *subsequent* pregnancy unless this occurs *many* years after an infection, when it is possible that the child might escape.

(*b*) If the mother becomes infected by the treponema at or near the time of conception she may exhibit no sign or symptom of syphilis and may enjoy a perfectly normal pregnancy yet her child may be born syphilitic, and her own positive serological tests will show that she has latent syphilis. She is in effect a Colles mother This type of infection I have for many years called conceptional syphilis.

(*c*) If the mother becomes infected during the period of gestation, she will almost certainly pass on the infection to the embryo or foetus as a post-conceptional syphilis, unless infection has taken place so late in the pregnancy possibly 6 to 8 weeks before delivery that there has not been time for the treponemata to cross the placental barriers.

Why expectant mothers so frequently have a subclinical form of syphilis is one of the unsolved problems of syphilology though several theories have been advanced for its explanation Rietschel (1912) suggested that it was due to the lodgement of the infected semen in the body of the uterus where the epithelium is columnar in type and where the effect is different from that produced when the stratified epithelium of skin or vagina is invaded. In the former event no primary or secondary lesions are manifested and a much milder form of the disease is produced Rietschel based his hypothesis upon the experimental work of Neisser who in monkeys, found that by different modes of inoculation—subcutaneous, intraperitoneal and intravenous—very different results were produced, from complete failure to infect by intraperitoneal infection, to generalized syphilis after intravenous injection

Brown and Pearce, in an experimental inquiry into the reaction of pregnant and lactating rabbits to inoculation with *T pallidum*, found that if the infection occurred practically simultaneously with conception little or no clinical sign of infection appeared—reproducing the condition shown clinically in a Colles mother Moore in his paper on Studies on the Influence of Pregnancy in Syphilis stated that pregnancy masks the symptoms of syphilis, as Brown and Pearce had shown experimentally in rabbits, the secondary or constitutional symptoms not appearing until the end of lactation So in pregnant women says Moore, the constitutional symptoms may be very mild and may be considerably delayed.

Little definite is known of the protecting power of pregnancy According to Routh it is due to the action of chorionic ferments though this view lacks support to-day in the absence of evidence of the existence of such ferments. Oestrogenic hormones may be one of the factors concerned in the modification of the course of syphilis in the pregnant, and in its milder course in the non pregnant, female, though how they act is not yet evident. This seems to follow from the experimental work of Frazier and of Kemp and their co-workers, who found that oestrogens modified the course of syphilis in male and female rabbits. The prompt appearance of these hormones in the urine of pregnant women shows how early in pregnancy their suggested moderating influence may be brought to bear upon the development of the disease. Chemical alterations in the blood and tissues of the pregnant woman and the lipoid concept of Burke have also been suggested as possible factors. On the other hand, some authorities (Fournier (1898) Bertin Klaften, Loe Ping Kian *et al.*) are of the opinion that pregnancy exerts a baleful effect on syphilis, rendering its lesions more extensive and destructive than usual and at times reactivating a negative serological reaction Anwyl Davies, in his book on Primary Syphilis in the Female," mentioned that many authors have drawn attention to the harmful effects of pregnancy on syphilis but that this did not accord with his experience My own experience has been that many of the mothers of syphilitic infants, especially primiparae have gone through their period of gestation without the slightest sign of syphilis and have evinced great surprise when told that they as well as their infants, needed treatment for their blood infection.

(4) Pre-parturitional transmission from mother to foetus

Already in 1876 Robert Cory had made the suggestion, which received the support of W S Greenfield, that an infant might acquire the infection from its mother shortly before birth, when—to quote his own words—

at the time of the separation of the placenta, before the foetal circulation has ceased, some of the mother's blood may be swept into the foetal circulation along the umbilical vein. If this be so it will also explain why the liver is so early and seriously affected in infantile syphilis. This view is supported by the observation that the incubation period is not far from coinciding with, though a little shorter than, the ordinary incubation period of acquired syphilis. Rietschel in 1912 revived this suggestion of Cory and at that time thought it explained the origin of many cases of congenital syphilis. Subsequently (1927) he modified his view and although he then considered that Cory's suggestion might apply to an occasional case of the disease, he thought infection was more frequently brought about during the actual birth process when treponemata, in large or small numbers, were able to pass from the diseased placenta to the

foetal circulation contributory factors being mechanical pressure from *uterine contractions and slight damage to the local tissues. It is even* possible, says Rietschel for an infant to have remained uninfected *in utero* and to be thus infected at birth.

(5) Parturitional skin infection

In addition to the foregoing pre parturitional blood infection there is a parturitional skin infection which is presumed to occur during the actual passage of the foetus from the uterus to the outside world These cases are rare, for certain conditions must be fulfilled for such infections to be possible firstly the mother must have a contagious lesion of the genital canal and secondly the child must not be syphilized or immunized. These conditions are realized only when the birth takes place during the first 10 to 12 days of the mother s chancre (Bonnet). In these cases the child s chancre is usually on the vertex *occasionally on the neck.*

(6) Infection via the mother s milk

Although formerly this figured prominently among the possible modes of infection of the offspring it needs little consideration at the present time. Mother's milk plays a very minor part, if any in the transmission of the disease.

The infectivity of milk. In the days when the utilization of wet nurses was common the question whether the milk of such nurses was infective, should they themselves be suffering from syphilis was one of considerable practical importance. Lancereaux in his treatise on syphilis (of which an English translation by Whitley was published in 1869) devotes two pages to the subject. There were two schools of thought the larger including many of the well known older syphilographers—Paracelsus Ambroise Paré Astruc, Bertin, Robert and others, who believed in the transmissibility of syphilis via the milk others among whom may be mentioned Hunter Swediaur and Ricord, who denied that milk might be a source of infection As Lancereaux points out, the milk itself may not be the cause of infection, but it may be the vehicle by which contamination from secondary lesions in the breasts or on the nipples of nurses or mothers is conveyed to a child. Diday had foreshadowed this view when he wrote in 1854 It remains established that the contact of the mouth of a nursling with the breast of a syphilitic nurse ought to be carefully avoided." Ten years later Lancereaux wrote Hitherto the absolute innocuity of the milk of an infected mother for a healthy child has not been clearly proved. Thus, it is not prudent to allow a child to be suckled by a syphilitic nurse if we wish to insure it against all danger

This indecisive state of affairs continued until the discovery of the spirochaete of syphilis and of its infectivity for the lower animals was

made in the early years of this century Since then a few observers (Lange, Uhlenhuth and Mulzer (1913)) have demonstrated the infectivity of milk by inoculation into rabbits testicles. From the demonstration that mother's milk may be infective though this is by no means always the case, it does not necessarily follow that infective milk can be secreted by the mammary gland. The milk when secreted may be sterile and the treponemata added as contaminants from a lesion in the main duct or on the nipple. The subject is of some practical importance to-day when milk banks are being established for the artificial feeding with human milk of immature and other delicate infants. A syphilitic mother with a positive W.R. in her blood may furnish a milk which likewise gives a positive reaction. This is of no importance provided the treponema is not present in the milk, which fortunately is not a frequent occurrence. Furthermore, the bringing of the milk to the boiling point would be sufficient to kill any parasites present (including the *M tuberculosis*) and subsequent cold storage would further ensure the death of the *T pallidum* and the innocuousness of the milk. Whether from the point of view of its chemical composition milk from a syphilitic mother is a perfect or even a good food for an immature or sick child is perhaps open to question. Lancereaux states that Vernois and Becquerel during the course of researches into the composition of the milk of mothers in health and disease, found that the milk of syphilitic mothers was grossly deficient in fat, contained an undue proportion of salts and the specific gravity attained an extraordinary height. I do not know if these findings have been confirmed.

In several families which have been under my care an apparently healthy child with a negative serological reaction has been suckled with impunity for periods varying from 3 to 6 months by a mother with a positive Wassermann reaction. My view is that if the mother's infection is comparatively recent, up to 2 years old, for example, the infant is almost certain to be syphilitic should the mother not have received treatment during pregnancy so there would be no additional risk in her suckling her child Should the mother's infection be of the late latent type, it is unlikely that she will be secreting treponemata in the milk.

Familial Infection

It is probably correct to assume that in the majority of instances syphilis is introduced into a family by the father who has usually contracted the disease before marriage. In one's own hospital practice it was often difficult to persuade the father to attend the clinic because of loss of time from work and the cost of travelling, though one sometimes found ways of overcoming these difficulties. It is important to interview the father in cases of syphilis in children in order to obtain a history from him to take a blood test and to form an opinion as to his credibility should he deny

any knowledge of having had the disorder In that event, admission of an earlier gonorrhoea or of premarital intercourse will make acquired syphilis a possibility or even a probability During and after the first world war one came across men with syphilis some of them apparently credible persons who did not admit sexual intercourse or promiscuity One came to the conclusion that under the conditions of static trench warfare, with the troops often infested with lice and other vermin, an innocent *infection with syphilis might possibly have been conveyed to healthy* men from a patient who was suffering from a syphilitic treponaemia.[1] Tattooing may I think, also be a means by which an innocent syphilitic infection may be acquired as was probable in at least one of my cases. Syphilis if acquired in either of these ways might fail to show primary and even secondary manifestations, so that the man would resemble a Colles mother in being entirely ignorant of the fact that he was a victim of the disease. Or on the other hand there might be mild primary and secondary lesions which under wartime conditions could well be overlooked Another relevant question is the father s occupation though this is probably not so applicable to-day as it was, say 40 or 50 years ago. At that time if a man had been a sailor or soldier and particularly if he had been in India or the Far East, he would almost certainly have contracted syphilis whether he admitted it or not. In those days we had no serological reactions to help us so service in the Army or Navy always connoted venereal disease—doubtless an exaggeration but a useful working rule![2]

If a father at the interview is unco-operative and refuses to have a blood test taken even though it is pointed out to him that the investigation will almost certainly be of benefit to his child, one may reasonably assume, in *the large majority of cases correctly* he has *concealed something* and that in all probability he has knowingly suffered from venereal disease It must be admitted however that the fathers of syphilitic children often give negative serological reactions and quite honestly have no knowledge of their having a syphilitic infection. To all intents and purposes they are carriers of the treponema. Jeans and Cooke (*op cit* p 67) found that more than 40 per cent of the fathers in their series of cases were serologically negative, frequently even with an admitted syphilitic history Of 187 fathers tested in my clinic 62 per cent were negative. Three possible explanations for this result suggest themselves. A small proportion had been thoroughly treated in the past and were cured Of the rest in some the infection might have died out others might still be harbouring the treponema and apparently living in harmless symbiosis with it. Yet

[1] The blood invasion by the treponema is called by Christian (in Osler s "Medicine" 16th Ed 1946)—no doubt correctly—a treponemataemia. This is a difficult word to negotiate so I have ventured to coin and use in its place the word treponaemia to designate a blood invasion by *T pallidum*.

[2] An occupation which during the second world war exposed many men and women to the risk of venereal infection was long-distance lorry-driving

in either of these two last eventualities, the relentless slow degenerative or inflammatory reaction of their tissues to the treponema will ultimately strike down some of these men with aneurysm or other cardiovascular catastrophe or with tabes dorsalis or general paralysis.

With the mothers the findings are very different. Table 6 shows the difference in the W R. of the mothers according to the ages of the children whether below or above 2 years of age One explanation of these findings

TABLE 6

Showing the W.R. of Mothers according to the Ages of the Children

	Mothers of children of ALL ages		*Mothers of children under 2 years*		*Mothers of children over 2 years*	
	Number	*Per cent positive*	*Number*	*Per cent positive*	*Number*	*Per cent positive*
Nabarro	453	90·5	240	98·7	213	81·2
Jeans and Cooke	647	86	383	93	264	76

is that presumably the infection is of the longest standing in the father more recent in the mothers of children under 2 than in those of children over 2, and that the serological reactions tend to weaken and ultimately to disappear as the infection becomes senescent.

Most of the mothers seem never to have any manifestations of active syphilis (other than the begetting of syphilitic children), yet ultimately a number as many as 30 per cent according to some authorities, develop general paralysis, tabes dorsalis, aneurysms or gummatous tertiary lesions.

In taking the history of a syphilitic family it is important to include an inquiry into the welfare or fate of the grandparents and *their* children—the patient s uncles and aunts—for by so doing one can not infrequently ascertain that one or other parent of the syphilitic child under investigation is a congenital syphilitic. This will be more fully considered under Third-Generation Syphilis (p 382)

Duration of the infectivity of parents

It is generally held that a man whose infection is of more than 5 years duration is unlikely to infect his female partner whether or not he had received treatment for the disease This is not invariably the case however for I have seen instances where a husband had infected his wife 10 or more years after he had contracted syphilis. On the other hand once a woman has become infected she can give birth to a syphilitic child during the whole of her child-bearing period, even 20 years after her infection, as in a case quoted by Boas and Gammeltoft. My belief is that if a congenitally syphilitic woman is given no antispecific treatment she may go

on bearing syphilitic children to a healthy man during the whole of her reproductive period

How does it come about that a man with quiescent latent syphilis infects his wife? Suspicion naturally falls upon the seminal fluid and the earlier investigators turned their attention to this secretion but at first without success. Treponemata could not be demonstrated in the semen and Neisser and Hoffmann failed to infect apes with semen obtained from syphilitic patients Other investigators, however (Pinard and Hoch and others) were able to demonstrate the syphilitic virus in the semen, and Finger and Landsteiner and Uhlenhuth and Mulzer infected animals with semen derived from syphilitic patients Under natural conditions of infection the treponemata may come not only from the secretion of the testis but also from the prostate and the seminal vesicles, and marital infection of the partner is much more likely to occur in the natural course of events than are treponemata to be found in an isolated experimental investigation of the seminal fluid. Matzenauer drew attention to the similarity between syphilis of the placenta and syphilis of the testis, in that if the epithelium of either organ is damaged the treponemata can pass, in the one case from the mother to the foetus and in the other case into the seminal fluid (Rietschel, in Jadassohn *op cit* p 23 footnote) In the early days of experimental syphilis Neisser had shown the predilection of the treponema for the testis, and the painstaking anatomical researches of Warthin demonstrated syphilitic lesions in the testis in 31 out of 36 autopsies although only 16 of the patients were known syphilitics, and all of them had been treated.

Two instructive cases may be quoted from our series in which unusually long periods of infectivity were exhibited by the father in one case and by the mother in another

Family 65 The father was infected with syphilis at about 20 years of age, and he was treated with mercury and iodoform for 9 months. He married in the year 1900 13 years after the infection yet he was able to infect his wife, for a daughter born the following year was treated in infancy for congenital syphilis and was later mentally deficient. When seen by us at the age of 26 years her W R. was negative but the Kahn test strongly positive. The mother had 5 subsequent premature births (at 7½ months) at intervals of about 2 years, the infants all dying at periods varying from 6 hours to 27 days after birth. Eventually a living boy was born, 18 years after marriage and *31 years after the father's infection* He was syphilitic and his history is given under "Liver (p. 169), since he first attended the V D clinic from Dr Cockayne's outpatients' department suffering from cirrhosis of the liver His father was then still alive and apparently quite well at the age of 65 years, yet we found his W R. was still positive (4-4-4-1) 45 years after the onset of his syphilis. The mother's blood was strongly positive at the age of 51 years, 28 years after marriage when presumably she was infected by her husband

In *Family 744* the mother was twice married in 1910 and 1919. She became infected by her first husband after the birth of a healthy child in 1911 She

then had 4 syphilitic children born either prematurely or at term, all of whom died young. Thereafter she had 2 healthy children, still by the first husband. After her remarriage in 1919, she had 3 healthy children by the second husband and then—*20 years after her original infection and after the birth of 5 healthy children*—she bore a syphilitic child with a strongly positive W.R. When this child was 2½ years old the mother's W.R. was found to be negative, but the Kahn strongly positive. Finally at the age of 43 years, she bore a twelfth child whose W.R. was negative and who showed no infantile symptoms of syphilis.

The transplacental mode of infection

The *Treponema pallidum* is not a blood parasite as is, for example, the trypanosome, so that, except perhaps in the early febrile stage of the disease and while the exanthem is fully developed, the parasite will not be present in the circulating blood for any considerable length of time. It is probably on this account that infection of the foetus is more likely to occur when the mother's attack of syphilis is recent. In older maternal infections periodical showers of treponemata may descend upon and into the circulation probably from the lymphatic glands and lymphoid tissue, which appears to be the tissue most favoured by the parasite. It is likely that at the time of infection, especially if this be via the cervix uteri or uterine cavity the treponemata may lodge and multiply in the pelvic lymphatic tissue and glands, which serve as reservoirs for them. From here they may be liberated from time to time aided doubtless by the hyperaemia of these parts and displacement of the viscera which take place during pregnancy. In the early months of pregnancy the placenta and foetal membranes form an effective barrier against the passage of treponemata to the foetus. This protective property of the placenta during the early months of pregnancy is no doubt due in part, if not entirely to the layer of Langhan's cells, which is intact until about the fourth month of gestation, after which it begins to atrophy. From the fifth month onwards, with the barrier no longer functioning, the treponemata are enabled to traverse the placenta and so infect the foetus. This leads to the death of the foetus in many cases and explains the much higher incidence of still births in syphilitic than in non-syphilitic women. The death of the foetus may be brought about by the direct action of the treponema or it may be due to failure of nutrition resulting from syphilitic disease of the placental vessels. This may possibly affect the nutrition of the embryo or foetus in the early months of pregnancy and thus compass the death and early expulsion of the foetus, as some authorities maintain (Milian, McCord, Golay). Hoffmann (*loc. cit.*, p. 11) says that early abortions should make one think of syphilis as a possible cause, which statement I endorse.

According to Rietschel, the infection of the foetus with *T. pallidum* may take place in two ways:

(1) An infected embolus may reach the foetus through the umbilical vein, which would account for the frequency and severity of the

pathological changes found in the liver in congenitally-syphilitic foetuses and children

(2) By a gradual progression of the motile treponemata in the lymph spaces of the umbilical cord towards the foetus.

The first is the usual and more likely route, but Rietschel is of the opinion that the second mode of infection is not only possible but of frequent occurrence. Infection by both paths may occur concomitantly

The actual time of transmission of the treponema from mother to foetus is one of the unsolved problems of syphilology and doubtless varies in different patients and in successive pregnancies in the same mother Most modern authorities hold the view that the foetus is not infected before the fifth month of pregnancy since parasitological and pathological evidence of congenital syphilis has not, with rare exceptions been demonstrated in the foetus before that date but, as was mentioned earlier in this chapter there are still a few diehards who do not agree entirely with the modern views.

It is also worthy of note that the treponema could also travel by the haematogenous route (the umbilical arteries) from an infected foetus to its mother

Lastly it may be mentioned that Uhlenhuth and Mulzer were able to demonstrate experimentally for the first time the transplacental infection of rabbits with syphilitic material.

The syphilitic placenta and cord

The syphilitic placenta is usually described as being pale, bulky and greasy looking F J Browne has pointed out, however that these appearances are found only in the placentas of macerated foetuses, and that if the foetus reaches maturity and is born alive albeit syphilitic, the placenta may appear to be healthy both to the naked eye and microscopically In the investigation anent this subject carried out by Eardley Holland for the Ministry of Health, he found, in agreement with Browne that increased weight of placenta or increased ratio to the body weight of the foetus was not a sign of much value, for heavy placentas were found among the non-syphilitic foetuses and lighter placentas among definitely syphilitic foetuses The naked-eye appearances of the placenta and the cut surface he found to reveal nothing of note and certainly nothing characteristic of syphilis. Voluminous cotyledons, deep sulci pale placental tissue grey and greasy maternal surface fibrous areas unusual softness and friability all erroneously supposed to denote syphilis, may at times be found to occur singly or in different combinations in syphilitic placentas, but they are as commonly found in other conditions. The white infarcts which have been described as being common in syphilis are in fact rare (only 2 out of 30 placentas) and they are commoner in cases of nephritis (Holland)

The histological examination of the placenta is often of great value, and Holland found that in about 65 per cent of the cases of foetal syphilis the placenta showed changes which are highly suggestive and almost diagnostic. The villi are uniformly increased in size, with correspondingly diminished intervillous spaces, owing to an increase in the amount and density of the stroma, of the collagen fibrils and of the villous cells. The vascularity of the villi is greatly diminished, as the vessels may gradually become obliterated by fibrosis, the result of subacute inflammation (Browne). Other observers state that the vessels of the villi are obliterated by endarteritis. Holland never observed this and states that what vessels there are occur as small circular collections of endothelial cells. Three types of placenta were recognized (1) typical, in which all the villi were affected as regards increase in size, density of the stroma, avascularity and close packing (2) suspicious, in which the change was patchy there were groups of enlarged avascular villi, but the groups were neither so large nor so numerous nor were the villi so avascular as in the standard typical section (3) the normal or negative placenta. Holland found that of the placentas of 26 syphilitic foetuses only 16 or 61 per cent were typical 6 or 23 per cent, were suspicious, while 4, or 15 per cent, were negative. On the other hand, the placentas of 91 apparently non-syphilitic foetuses were typical in 5 and suspicious in 10

The American evidence upon this subject, which has been summarized by Whipple and Dunham in their review is rather at variance with the British views quoted above The ratio of placental to body weight is looked upon as significant. Whitridge Williams (1920) believed that the placental changes formed a basis for the diagnosis of congenital syphilis in 80 to 90 per cent of infants. Later investigators were less dogmatic in their statements (Jeans and Cooke, *op cit* p 21 McCord, 1928 and 1934 Ingraham and Kahler 1934) and more nearly approximate to the views of Holland and Browne.

Treponemata have been found by many observers in syphilitic placentas, but they are usually sparse, and much time and patience are needed to demonstrate them in stained sections. Most authorities say that the parasites are more numerous in the foetal than in the maternal part of the placenta, which is regarded by them as an indication that the foetal tissues are a better culture medium for the treponema than are the maternal tissues. On the other hand, Jeans and Cooke and other observers state that the treponema is more readily demonstrated on the maternal than on the foetal side, while F J Browne makes the statement that the treponema is practically never found in the syphilitic placenta and he adds The reason for this is not known The treponema can be found with much greater ease and certainty in many of the foetal organs.

The *umbilical cord* may furnish definite evidence of syphilitic infection. Early observers (Bondi Thomsen etc) described, at the ends of the cord

signs of subacute inflammation with leucocytes, small round cells or plasma cells in and around the walls of the umbilical vessels. These changes were seen more frequently at the foetal than the maternal end of the cord and by appropriate staining (Levaditi's method) *T. pallidum* may be found in considerable numbers in the tunica intima of the umbilical vein. Scrapings taken from this area will frequently show the presence of the treponema by dark ground illumination, sometimes even when the placenta is anatomically negative for syphilis.

Ingraham (1935) re-emphasized the value of this procedure in the early diagnosis of congenital syphilis, but in actual practice its application would be limited to clinics or institutions where the requisite pathological facilities were available. The finding of treponemata in the wall of the umbilical vein is almost tantamount to a diagnosis of congenital syphilis, but several observers have noted that failure to demonstrate them in the vein does not exclude syphilis in the infant.

Syphilis, fertility and sterility

Opinions differ as to the possible relation of syphilis to sterility. In this connection it must be remembered that syphilis may have been associated with gonorrhoea, to which the subsequent sterility was really due. Recent investigations into the causes of sterility have shown that non-syphilitic men and women may be sub-fertile, and it is not unlikely that if such individuals contracted syphilis some of them might become absolutely sterile. The Solomons (*op. cit.* pp. 116 and 120) give a table showing figures abstracted from the literature of the subject, varying from 4 to 75 per cent for the incidence of sterility occurring in syphilitic families, and from their own observations of the families of late neurosyphilitics, including paretics, they conclude that syphilis plays a large part in the production of sterility and childlessness. From the nature of one's own material, which has nearly always started with a congenitally syphilitic child, it is impossible to say if syphilis is a cause of sterility, though it may well be so; how often one cannot say. In a few families in my series pregnancy did not occur for as long as 8 years after marriage, but subsequently several children were usually born.

Diminishing severity of transmitted infection

A not uncommon obstetric history of a syphilitic mother is that she may be married 3 or 4 years before becoming pregnant, and have one or more miscarriages at 3, 4 or 5 months, to be succeeded by a premature syphilitic child at 7 or 8 months, then possibly a syphilitic stillbirth at term or a syphilitic infant dying shortly after birth. The next child may be born healthy but sicken at the age of 3 to 6 weeks or even later. This attenuation of syphilis by efflux of time was noted by Diday (1854). Jons

than Hutchinson in 1865 and by Kassowitz in 1876 Kassowitz law states that the older the infection is in the parents the less serious are the effects on the children, though it is uncertain whether this diminution in the intensity of the infection is to be attributed to the father to the mother or to both parents. However it will have been inferred from observations made earlier in this chapter that most authorities would regard the beneficent effect of repeated pregnancies upon the mother as being the most likely factor

While the complete sequence of obstetric disasters cited may have been usual in the past, it certainly has not accorded with my own experience in which the patient seen at the clinic has often been the result of the mother's first pregnancy Admittedly some of the older mothers did give a history of having had one or more stillbirths and neonatal deaths before the birth of the living syphilitic child.

Increasing severity of transmitted infection

One has encountered several families in which as the result of a certain amount of treatment of the parents a healthy child has been born but subsequent children have been infected in an increasing degree. This sequence of events does not appear to have been emphasized by syphilologists. The explanation appears to be that the parents had not been given sufficient treatment to effect a cure, and in the cases I have come across they had not undergone a spinal fluid test. In consequence, owing to the gradual waning of the effects of treatment whereby a relapse or recrudescence of the disease occurred in one or both parents the later children suffered a gradually increasing severity of the disease. In an illustrative family in my series, after the birth of a healthy child shortly after the treatment of the parents, the second and third children had slight symptoms the third child more than the second, sufficiently suggestive of congenital syphilis to justify treatment. This was given at a general hospital and took the form of hydr cum cret., upon which the child got well. No blood tests were taken. The next child had frank congenital syphilis, for which it was brought to Great Ormond Street. A careful familial investigation revealed that all these children had positive serological reactions in their blood and cerebrospinal fluid and that the parents blood had relapsed, having previously been reported negative.

As regards *fertility* syphilitic mothers, once they have successfully overcome the initial sterility stage, appear to have more pregnancies than healthy mothers. The reason doubtless is the fact that so many of the syphilitic pregnancies end in disaster before term. Harman's figures given in Chapter 3 show this, and Jeans and Cooke (*op cit.*, p 97) state that in 250 syphilitic families an average of 5 8 pregnancies occurred as against 4·9 per family in 350 healthy families. The Solomons on the other hand, found (p 126) that the average number of pregnancies per

family in their group of 555 syphilitic families was 2 58 a figure much lower than that given in the studies referred to above. It is important to bear in mind the observation of Jeans and Cooke, the Solomons and others that the discrepant figures for fertility data and for the numbers of infected and healthy children in syphilitic families reported by different authorities are dependent upon the different methods employed for detecting a syphilitic family—whether by a syphilitic father an infected mother or a congenitally-syphilitic patient.

Profeta's law It is often stated that Profeta's law asserts that the healthy child of a syphilitic mother is immune to syphilis. This imports into Profeta's observations considerably more than was originally there. Profeta said that the healthy child of a syphilitic mother could be suckled by her or by a syphilitic nurse with impunity (cited by Ogilvie). Later writers commenting upon Profeta's dictum enlarged its scope, so as to emphasize the analogy of the Colles mother who was likewise considered to be immune to syphilis. Since the discovery of the Wassermann reaction we know that the so-called immunity of the Colles mother is simply the expression of the resistance of an infected person to a super or re infection. Similarly the apparently healthy child of a syphilitic mother who cannot be infected by her or by a syphilitic wet nurse as Profeta stated, we now know to be a latent syphilitic with a positive serum reaction A child who appeared to be an exception to Profeta's law would doubtless be one who was before its postnatal infection, the *healthy* child of its syphilitic mother It might be difficult, however a little later in life, to distinguish such an infantile infection from a late antenatal infection

Twins in syphilitic families

A Fournier (1891) stated that in his experience the frequency of twin births in syphilitic families confirmed similar statements made in the literature. In his opinion the association was too frequent to be purely coincidental He writes Syphilis certainly gives rise to twins, but I do not know why or how Other French writers have confirmed Fournier's dictum, but v Zumbusch (in Jadassohn, *op cit* p 273) regards this view as an exaggeration or as he says, those who hold that syphilis favours twin pregnancies put the case too strongly My own inquiries into the histories of more than 400 families have resulted in the finding of 23 pairs of twins and 2 sets of triplets in about 2,000 pregnancies. The number of twins is not abnormal but the triplets are above expectation, though with only 2 sets their occurrence may be accidental and unconnected with syphilis It is noteworthy that in our series no mother had borne more than one pair of twins

Transmission to twins When twins are born to a syphilitic mother the disease may affect one or both infants. With uniovular twins both are

probably always affected for as Jeans and Cooke say (*loc cit* p 71), it would apparently be impossible for one twin of the uniovular type to escape the disease if the other were infected *in utero* since their bloods commingle. Clinical observations have confirmed the contingency that such twins always share the same fate. On the other hand Erich Hoffmann (*loc cit* p 11) states that twins may be unequally affected by syphilis to the total exclusion of the disease in one of them, even if they be uniovular He refers to such a case which he regards as being due to a focal syphilitic inflammation of the placenta and umbilical cord. Penrose, who reported an instance of identical twins with dissimilar serological reactions, explained it by suggesting that environmental conditions *in utero* were more favourable to one foetus than to the other Wolk has also reported a case of identical twins aged 19 both of whom had undoubted congenital syphilis, but in one of them the W R. had become negative. Several authorities (Harrison, Wile and Welton, Dennie and Pakula and others) have reported that of twins one may be positive and one negative.

The majority of the twins in my syphilitic families escaped the infection Five of the twins were definitely syphilitic. The first pair were almost certainly identical twins both were infected but only one showed a syphilitic lesion (Clutton, right knee) They responded serologically to treatment in an identical manner The second pair were possibly identical twin boys, for the medical officer of the hospital at which they were born reported on inquiry that there was only one placenta one infant was infected and died at the age of 4 months, the other was healthy when last seen (at 3½ years, when he defaulted) The other 3 pairs of twins were all binovular the 3 male children were all infected, 2 survived the third died of whooping-cough at 1 year Two of the 3 twin girls were infected. One died of whooping-cough at 1 year and the other died from severe involvement of the central nervous system.

Of 18 other syphilitic families in which twins occurred the chief points of interest were (1) several of the twins were stillborn or died very young so that they could only be graded probably or possibly syphilitic (2) in 4 of the families the mothers were themselves congenital syphilitics.

The determination of uniovular or monozygotic twins is very difficult and in many cases wellnigh impossible as may be inferred from the formidable list of requisites to be fulfilled given by Wile and Welton in their paper referred to

Of the 2 sets of triplets in my syphilitic families, there was only one survivor and he was infected The 2 siblings died at birth and in 6 days respectively As regards infection they should be classed as probably syphilitic (*b*). The survivor was thought to be suffering from icterus gravis and his case was described as such by Hawksley and Lightwood The other set of triplets were all stillborn at the sixth month. They

resulted from the first pregnancy by the mother's second husband and were born about 4 years after the birth of her previous child who was a congenital syphilitic. The triplets should probably be placed among the possibly syphilitic (c)

The prevention of transmission by treatment of the parents

It is almost axiomatic that parents, whilst they are still in the infective stage of syphilis, should not beget children, though it is difficult to fix a definite date for their freedom from infection. It varies from patient to patient, with the age of the infection in the parents and with the nature and duration of the treatment they have received. In the pre penicillin era it was considered safe, from the offspring's point of view if the parents had received at least a full course of neo-arsphenamine and bismuth or mercury treatment as detailed later (Chapter 12) and had negative serological reactions in the blood and cerebrospinal fluid. If pregnancy supervened shortly after the cessation of treatment the blood should be tested at monthly intervals, and at the first sign of a serological relapse a fresh course of treatment should be begun and a repeat blood test taken a month after the end of the course Further treatment during the pregnancy would depend upon the result of the blood tests.

Following the finding of a positive blood test in an expectant mother on confirmation of the result, antisyphilitic treatment should be instituted as soon as possible. At the present time it is the custom to give penicillin in association with arsenic and bismuth, as is done in this country (Mac farlane 1950) or penicillin alone, as is done in America (Goodwin and Moore, 1946).[1] Formerly the ordinary treatment with neo-arsphenamine and mercury or bismuth was given in the usual dosage, for it was found that expectant mothers were more tolerant of arsenic than were non pregnant women. My own practice has been to allow a monthly interval between the courses as in the treatment of an ordinary case of syphilis, though some authorities gave continuous treatment throughout pregnancy with alternate courses of arsenicals and bismuth, in either case continuing the treatment as long as possible until term. Although it is desirable to initiate treatment as early as possible in the pregnancy to secure the *birth of a healthy infant no matter how far advanced in pregnancy a* woman may be when her blood is found to be positive appropriate treatment should be given. A healthy child may be born after even a few injections, but such a fortunate result does not necessarily prove that it is due to the treatment given, for it is common knowledge that, even without antisyphilitic treatment, a healthy infant may be born to a mother whose blood test is positive. Most authorities recommend

[1] Also several other authorities mentioned in the *Transactions* of the Helsinki Symposium, 1950 pp 86–88 referred to on p 417

that a mother who is known to have had syphilis or a positive blood test should be treated in *every* subsequent pregnancy even if her blood then be negative (Cole *et al* 1936) whereas Goodwin and Farber came to the conclusion that provided a mother had previously been adequately treated and her blood was serologically negative or only slightly positive, it was probably safe to allow her to go through a subsequent pregnancy without further treatment. (See Chapter 12)

Third-generation syphilis

Syphilologists have long been interested in third-generation syphilis The subject is dealt with fully in Chapter 9.

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CHAPTER 5

PATHOLOGY

The causal organism

THERE is no longer any doubt in the minds of most authorities that all stages and types of syphilis are due to the *Treponema pallidum* (syn. *Spirochaeta pallida*). Morphologically in the discharge from syphilitic lesions examined fresh under dark-ground illumination the treponema resembles a tightly-coiled spring from 4 to 14 μ long with from 8 to 12 or more regular tight coils which become rather shallower and more opened out towards the ends. The parasite gradually thins as the ends are approached and Schaudinn figured the ends prolonged into a fine thread like a flagellum. Its movements are complex (1) a to-and fro movement with either end foremost (2) a rotatory or boring movement round its long axis and (3) an active bending on itself to form a V or even a circle. Notwithstanding its local activity its rate of translation is relatively slow so that it is not difficult to watch an individual parasite for a considerable time under the microscope.

Modern methods of investigation, the dark-ground and electron microscopes, supplemented by the ultraviolet and phase-contrast photography have revealed a structure common to all the spirochaetes hitherto examined, and according to Bradfield and Cater found in no other organisms, which serves to place the spirochaetes in a distinct group based upon their unique structure. This consists of (1) a protoplasmic core, (2) a spirally wound bundle of fibrils, and (3) a cell membrane, which may have the bundle of fibrils either within itself or wound round it externally By mild tryptic digestion Bradfield and Cater were able to recognize the three components in *T duttoni* of African tick fever *T recurrentis* of relapsing fever and the cultured, pathogenic Nichol strain of *T pallidum* Schaudinn depicted a parasite with two flagella at one end which he thought suggestive of longitudinal fission. In Chapter 4 it has been stated that Levaditi Metrowsky and others have described varied forms, some of them probably evolution forms, others possibly degeneration products. McDonagh's developmental forms of *Leucocytozoon syphilidis* lack confirmation but Metrowsky's findings of branching and budding forms were confirmed by DeLamater and his associates by means of phase-contrast microscopy We frequently found that the treponema could not be demonstrated post

mortem in the organs and tissues of our patients this we attributed in part to the treponemicidal effect of the drugs used in treatment and in part to autolysis or breaking down of the parasites into unrecognizable and possibly ultra microscopic forms

In the absence of facilities for dark ground illumination the treponema *can be demonstrated by mixing fluid expressed from an active lesion such* as a primary chancre or in a case of congenital syphilis, a condyloma, with Indian ink, spreading on a slide like a blood film and allowing the film to dry The background is greyish-black or brown, and the parasites appear as white corkscrew like spirals. Staining of the parasites may be done with Giemsa or by Leishman, which stains them a pale reddish mauve. Silver methods (Levaditi Bertarelli and Volpino, Wharin Starry Jahnel Steiner) can also be employed for showing the treponemata in secretions or tissues, but as these methods give rise to a deposit of silver on the parasites, these appear rather coarser than when examined either by the dark-ground or simpler staining methods.

When hunting the parasite care must be taken that the material examined is free from adventitious particles. The surface of the lesion should be swabbed with methylated ether which quickly evaporates, then lightly scraped with a sterile scalpel until a little fluid exudes. This fluid especially that from a condyloma is found to contain many treponemata, which can be demonstrated by any of the methods given above. Owing to the infectious nature of such lesions rubber gloves should be worn during these manipulations.

The *T pallidum* is not a very hardy organism, as it dies in a few hours on infected linen or clothing it is also easily killed by weak antiseptics and by soap and water It can resist extreme cold but is rapidly killed by a moderate heat (40 –50 C).

Infectivity of syphilitic infants and children

The older writers reported numerous instances of the infection of contacts by syphilitic infants (see Chapter 4). Instances are also on record of wet nurses being infected on the nipple by suckling syphilitic infants. In view of the fact that the organs and tissues of such infants may be teeming with parasites, it is remarkable how seldom the disease appears to be conveyed to contacts. and in my own experience I have not come across a single case where, for example, a nurse has contracted the disease by contact with a patient. It is certain, however that the discharges from syphilitic lesions contain living and virulent parasites so that nurses should wear rubber gloves when handling syphilitic infants before and during the first 7 to 10 days of treatment. After a certain amount of treatment[1] has been given to these infants, and in the case of older

[1] By this I mean *adequate* treatment not homoeopathic doses of drugs, as was sometimes the practice even in hospitals.

children, the risk of infection is practically negligible unless there are sores in the mouth or condylomata on the surface of the body The mother of a syphilitic infant runs practically no risk of infection—she is already infected in the large majority of cases—but healthy sibs run a definite risk if they nurse, fondle or feed the infant. It is on record that pathologists performing autopsies on syphilitic infants have become infected as long as 48 hours after the death of such infants (Harrison)

The tissue response

The pathological changes which may occur in the organs and tissues of a syphilitic infant will be described under the individual organs concerned but a brief account of the reaction of the body to invasion by the *T pallidum* may be given here. From it the reader will be able to appreciate the fact that in the congenital, as in the acquired, form syphilis is still the great mimic of other diseases. The early stages of invasion in the two types of the disease acquired and congenital, differ until the treponema reaches the blood stream, and from that time onwards the reactions are similar In acquired syphilis the parasite, having gained access through an abrasion in the epithelium or mucous membrane, invades the depths of the tissues, boring its way between the cells, for which its corkscrew like shape appears to have been specially designed During this process it multiplies and travels by way of the lymph spaces and lymph channels to the regional lymph-nodes How speedily this may be effected will be realized from the finding of the parasite in the nearest lymph nodes of rabbits within half an hour of inoculation (Kolle and Evers, 1926) *T pallidum* favours the perivascular lymphatics and it soon enters the blood stream, with the result that long before the primary lesion (chancre) manifests itself the whole body has become infected by the parasite. In congenital syphilis this state of affairs may arise at any time during the last few months of pregnancy or at about the time of birth *directly* by way of the umbilical veins and without the intervention of a primary lesion. Clifford Allbutt introduced the term lympharteritis with its implication that the reaction to the treponema starts in the lymphatics of the adventitia of the arteries. The term lymphartentis has not been adopted by pathologists, which in my opinion is unfortunate, since it is a very descriptive term.

The local reaction to the treponema is the determination of lymphocytes and plasma cells—the characteristic cell of syphilis—to the perivascular lymphatics and hence to the small blood vessels themselves. Being an anaerobe the parasite is not happy in the oxygen-containing blood and therefore leaves the circulation as soon as possible to find a more congenial medium in the endo- and perithelia of the blood vessels and lymph spaces, and in the walls of the blood vessels, often around their *vasa vasorum* At times the lumina of the affected blood vessels may be

partially or even entirely occluded Later on fibroblasts give rise to increased collagen fibrils and fibrosis is a marked feature of the late stages of the syphilitic reaction. The tertiary lesions in addition to being fibrotic are often gummatous in nature, the gumma being a granuloma consisting of lymphocytes, plasma cells, epithelioid and giant cells. In structure a gumma resembles a miliary tubercle or tuberculous granuloma but the giant cells are smaller and less numerous than in a tuberculous lesion, and of course no tubercle bacilli are to be found in a pure gumma. Syphilomata or gummata of lymph nodes are sometimes mistaken for tuberculous adenitis (see p 268). Gummata frequently undergo necrosis and if superficial they may give rise to characteristic sloughing ulcers with serpiginous outline. They are hardly if at all infective, in contrast to the primary (chancre) and secondary lesions (rashes, mucous plaques, condylomata) which are highly infective.

It was mentioned above that congenital (antenatal) syphilis differs from acquired syphilis in that the congenital patient has no primary lesion There are two other important differences first, the foetus appears to afford a favourable soil for the multiplication of the treponema, since most of the foetal tissues and organs usually swarm with parasites and secondly the foetal organs and tissues being immature when they are smitten by the infection are often retarded in their development or they may become dystrophic and never attain their full normal development. Hutchinsonian teeth and mental and physical infantilism are examples of disordered or retarded development. These effects may be due to the direct action of the treponema (or its toxin) upon the growing tissues and the resulting mild but chronic inflammatory reaction going on to an inexorable fibrosis. Circulatory disturbances consequent upon endarteritis, and giving rise to serious interference with the nutrition of organs, especially the brain heart, liver and endocrine glands, may also play a part. Finally if as has been suggested in Chapter 4, a true inheritance occurs as in syphilis of the third generation it is further possible for the developing ovum to be so adversely affected by the contained treponema or an evolutionary phase, that a congenital malformation or even a monstrosity may ensue.

Diagnosis of congenital syphilis after death

(a) *In the foetus* In the past it was generally held that a macerated foetus was nearly always syphilitic. It is now known that in severe forms of erythroblastosis foetalis (see p 242) a macerated foetus may also be expelled from the uterus and in practice it may be difficult to decide which of these causes has been operative. A relatively large placenta is *often* relied upon to diagnose syphilis but it is stated by Eardley Holland F J Browne and others to be unreliable for the diagnosis of syphilis in any particular case. The various other criteria by which it was stated a placenta could be diagnosed as syphilitic such as hyperplastic villi of

diminished vascularity pallor of the placental tissue, large cotyledons, fibrosis and the presence of infarction, Holland refuses to accept as evidence of syphilis. Henderson in a paper on Erythroblastosis gives various criteria by which the condition may be diagnosed from syphilis but in actual practice differentiation is difficult. Treponemata disintegrate quite early in macerated foetuses (McIntosh) therefore their recognition in the placenta or in the foetal tissues cannot be relied upon The liver may be enlarged and show intercellular fibrosis in both diseases. The spleen may show diffuse fibrosis in congenital syphilis, but only rarely does so in erythroblastosis foetalis. Even the changes in the long bones the deepening of the zone of provisional calcification, cannot be relied upon to differentiate the two diseases, as Caffey Gilmour and others have shown. Unless, therefore, the long bones show unequivocal signs of syphilis, such as cat bite lesions of the tibiae (see p 201), saw tooth metaphyses, epiphyseal separation and so forth, evidence of syphilis must be sought in the parents or sibs (anamnesis, blood test)

(*b*) *In infants who have survived birth* Recognition of congenital syphilis in an infant who has survived birth may be confirmed in one or more of the following ways

(1) Examination of the skin for evidence of pemphigus or other syphilitic eruption and if such be found, examination for the treponema in scrapings by one or more of the methods mentioned earlier in this chapter

(2) X ray examination of the limbs for the presence of unequivocal evidence of syphilitic osteochondritis

(3) Examination of the internal organs and viscera (*a*) in smears for the treponema, (*b*) in sections by Bertarelli and Volpino s or by Leva diti s method, and (*c*) sections of liver lung pancreas and testis for interstitial fibrosis.

(4) Removal and examination of a longitudinal section of a tibia and or lower end of a femur for the presence of the typical cat-bite lesion at the upper and inner aspect of the tibia (see p 203) and/or the characteristic irregular yellowish or grey epiphyseal line at the lower end of the femur

For the examination of bones Turnbull gives the following instructions

For microscopical examination, except when it is desired to stain spirochaetes, the minimum of decalcification compatible with section should be employed recognition of the distribution of the provisional calcification in the epiphysis is as important in microscopical examination as in the macroscopical. Foetal bones fixed in 4 per cent formaldehyde and embedded in paraffin or celloidin can be cut on the microtome without decalcification It is important to remember that the calcium in bone is not stained by haematoxylin unless the bone has been fixed for at least a week

in formaldehyde solution or in Müller's fluid. If the spirochaetes have not been destroyed a certain diagnosis can be made with great rapidity by examination with dark ground illumination of scrapings from the metaphyses of suspected bones which have not been placed in any fixative.

Finally it may be mentioned that post mortem Wassermann tests are unreliable, since the blood serum is frequently anti-complementary and "false negatives" and "false positives" are liable to occur.

Serological Reactions

The serological reactions for syphilis include the Wassermann reaction, with its various minor modifications, and the many flocculation tests—the Kahn, Kline, Sigma, Meinicke and others, the technical details of which cannot be discussed here.

Although the W.R. has been utilized in the diagnosis of syphilis for nearly 50 years, the biological basis upon which it rests is still uncertain. Developed as it was from the *immunity* reaction of Bordet and Gengou, the antigen used originally was prepared from syphilitic organs and the reaction was consequently considered to be a *specific* one. When, however, it was found that extracts of healthy organs, notably ox heart, could furnish an antigen as good as or even better than one made from syphilitic livers (Marie and Levaditi, 1907), the specific nature of the reaction had to be modified, but the W.R. remained, and still is, a valuable aid in the diagnosis of syphilis. The reaction must, however, be properly carried out. Harrison's article on "Syphilis" in the Medical Research Council's "System of Bacteriology" gives some idea of the amount of research that has been devoted to the complement fixation and flocculation tests, and the research is still going on 20 years since Harrison wrote the article, yet many pathologists who profess to carry out the test often do so in a somewhat perfunctory manner. A reliable report on the W.R. is of so much importance to the patient, to his family and to the State that it behoves all who participate in the performance of the test—from the taking and labelling of the patient's blood or spinal fluid, performing the technical procedures, to the final typing-out of the report—to do their utmost to secure accuracy in the performance of their particular contribution to the test. A positive report which is incorrect may mean much mental anguish to the patient, often leading to domestic unhappiness, and necessarily gives rise to much treatment, trouble and expense. All this can be avoided by adopting the practice, before reporting a positive result, of repeating the W.R. upon another specimen of the patient's blood. On the other hand, an incorrect negative report gives the patient and his doctor a false sense of security and so leads to the loss of valuable time in treatment. Should the patient show signs or symptoms suggestive of syphilis, the blood test should be repeated during the course of the next 2 or 3 weeks,

and even if again reported negative, clinicians need to be reminded that a *negative W. R. may be returned from a case which is undoubtedly syphilitic* and that a therapeutic test may be helpful in establishing the diagnosis. The pathologist performing the test must ensure that his technique is not too sensitive so that non-syphilitic bloods are reported as positive, and that his method is not too insensitive so that syphilitic bloods are incorrectly returned as negative. A striking example of unreliable Wassermann reports is given in Chapter 3 (p. 47) where the antenatal testing of expectant mothers by *laboratories under the aegis of the same public* authority is stated to have yielded positive results ranging from 0·27 to 2·79 per cent over a period of 9 or 10 years, the patients belonging to an almost identical social status.

The system of control and supervision of the Wassermann and flocculation techniques which was suggested by Harrison and introduced in this country between the two world wars has unfortunately, doubtless for *reasons of economy*, been suspended. *This is greatly to be regretted and,* in the interests of the many who may be concerned, it is to be hoped that the system of control and supervision will be reintroduced at the earliest opportunity.

The actual techniques of the complement fixation (Wassermann) and flocculation tests cannot be described here and should be ascertained from special writings upon the subject, and the English reader is referred to Orpwood Price's *account of these tests, since he is now the Director of the* Venereal Diseases Reference Laboratory of the Ministry of Health, as well as being pathologist to a large London V.D. clinic. From one's own experience one would say that the only way to learn the technique of these tests is to watch them being properly done and then to practise them under the eyes of an expert until all details have been mastered, and finally to perform the test personally on the same bloods as the expert until the results eventually agree.

Collection of the blood for serological testing

To collect blood from a child any well fitting all-glass syringe is preferable to a record syringe with metal piston, since in the latter the piston is apt to work stiffly. The three piece all-glass (Agla) syringes formerly supplied by Messrs. Burroughs, Wellcome and Co. were used in the author's clinic for many years and were found entirely satisfactory both for the taking of blood for testing and for the administration of intramuscular and intravenous injections. 5 ml. syringes are the most convenient size, but for special purposes—small or large injections—3- and 10-ml. syringes may be found useful. During the 22 years that I directed the Clinic at Great Ormond Street the syringes were always sterilized by boiling them in distilled water. After boiling for ... or 3 minutes they were removed from the sterilizer with sterile forceps and placed on a sterile

towel. The needles,[1] with stylets removed, having first been tested to ensure that the points were not turned over either forwards or backwards, were immersed in the boiling water for 10 to 20 seconds only so as not to blunt the points, after which they were removed from the steriliser and laid beside the syringes on the sterile towel. When the syringe had cooled down it was emptied of water the needle attached and the syringe filled with sterile saline from a flask. The needle being firmly held by forceps, the saline was forced out through the needle and discarded. The syringe and needle were then ready for the taking of the blood.

N.B The syringe should *never* be washed out with alcohol, ether or any other antiseptic, for this would spoil the blood for the W R. nor should it contain any water which would cause haemolysis of the blood and likewise spoil it for the tests.

The same syringes were used for taking blood for testing and for giving injections of arsphenamines and bisoxyl and, so far as I am aware, no harm was ever occasioned in any of our patients by this method of sterilizing the syringes. The Medical Research Council has however recommended that all syringes should be sterilized by dry heat at 160 C for one hour or autoclaved at 120 C. for 20 minutes to avoid the risk of any virus infection being conveyed by them.

The blood may usually be obtained from a vein at the bend of the elbow but this may occasionally be difficult to carry out. Other veins which may be used are the external or internal jugular or a scalp vein. Following German authorities who state that, after the initial diffidence has been overcome, obtaining blood from the superior longitudinal sinus from infants in whom the anterior fontanelle is still open (usually up to 15 months) is quite easy I used the method for many years in my clinic without mishap [2]

Method of obtaining blood from the superior longitudinal sinus

Unless the scalp is very hairy no preliminary shaving is necessary The infant, wrapped in a blanket so that the arms are included is placed across a narrow cot or table (preferably the latter as it will not "give"), with the crown of the head facing the operator and the infant's nose directed vertically upwards (Fig 19). The skin over and around the fontanelle having been cleansed with iodine or other antiseptic, the nurse holds the head firmly in position with her hands on *either* side of the face. The head

[1] We used B W and Co's No 209 "Agla" hypodermic needle and for puncture of the longitudinal sinus with a rather short bevel. The dimensions should be length about 40 mm. (1⅝ in) bevel about 2 5 mm., and external diameter of blade 0·80 mm. (21 S W G)

[2] Most British authorities prefer not to take blood from the superior longitudinal sinus and utilize some other vein. See Cathie 1953 Garrod, Batten and Thursfield's "Diseases of Children" p 1904

should not be flexed or over-extended but the fontanelle should face the operator squarely The syringe with the needle attached is held in the right hand pointed *straight* at the *posterior* angle of the fontanelle and gently pressed through the skin the syringe and needle being steadied by the forefinger of the *left* hand by gentle pressure posterior to the fontanelle to prevent the needle penetrating too deeply As a rule the crying of the infant is sufficient to cause the blood to flow into the syringe, but should the piston not work as smoothly as is desirable it may be carefully with-

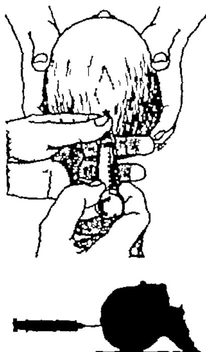


FIG 19 Illustrating the method for obtaining blood from the superior longitudinal sinus

drawn by rotating with the right hand in the barrel which is securely held in position with the left hand. When the requisite 5 ml. of blood has been obtained the syringe and needle are withdrawn and the nurse immediately takes the child in her arms to nurse it, at the same time applying a small wad of sterile cottonwool to the fontanelle. The infant ceases to cry as soon as it is nursed, and a small dressing of wool and collodion completes the operation.

Before transferring the blood to a sterile tube or screw-capped 25 ml bottle, the needle is removed from the syringe so that there is no risk of haemolysis, as might occur from rupture of the red corpuscles if the blood

were forced into the tube through the needle. After standing for an hour (or longer) to clot, the serum is pipetted off

Cord blood

It is sometimes recommended that umbilical cord or retroplacental blood should be used for serological testing This is valueless from the point of view of diagnosing syphilis in the foetus or infant, for McKelvey and Turner and others have shown that a positive result on the cord blood is not diagnostic of congenital syphilis, neither does a negative test exclude it.

Reporting on the Wassermann Reaction

The W R. having been performed by an approved technique (see Harrison-Wyler technique and O Price's method), the results may be expressed as "strong positive, positive, doubtful or negative." (The author's method of reporting on a W R. as used throughout his observations and also in this book will be recorded later)

Complement fixation versus flocculation tests

Following Harrison's lead we in this country prefer complement fixation methods (properly carried out) to any of the flocculation tests. The latter are easier and quicker to perform once a reliable antigen has been prepared, but require more experience in the final reading of them. Our experience has been that the Kahn test is more sensitive than the Wassermann test, so that it remains positive longer on a treated patient than does the W R. A special technique is required for flocculation tests on cerebrospinal fluids and we have no experience of their use with these fluids.

Personal methods employed in carrying out the Wassermann test and reporting the results

The method originally used was demonstrated to me by Prof H R. Dean, who was then working at the Lister Institute (he having learnt the technique from Wassermann himself) in which the dilution of patient's serum in the first stage of the test was 1 in 15 and 3 units of complement were added. Subsequently from 1919 onwards, the No 4 method suggested in the Ministry of Health M R.C Memorandum was followed. In this method the standard dilution of serum was 1 in 15 3 units of complement and a cholesterinized antigen were employed For treated cases the test was made quantitative by using higher dilutions of serum, 1 in 30 and 1 in 60 and 2 amounts of complement 3 and 5 units. In this way 4 or 6 tubes were used for the serum of patients undergoing treatment, with serum 1 in 15 1 in 30 and 1 in 60 dilution each with 3 and 5 units of complement The final volume of fluid after the addition of 1 ml. of sensitized corpuscles, was 2 5 ml and those tubes whose contents were *completely haemolysed* after being in the water bath at 37 C. for half an

hour were recorded as negative (0). The remaining tubes were kept in the refrigerator overnight or if an immediate reading was required were centrifuged at 2,000 revs. for 5 minutes. If the supernatant fluid showed no haemolysis, with the fluid colourless and *all* the corpuscles subsided the tube was called a 4; if half the corpuscles had subsided the tube was called a 2 and the numbers 3 and 1 were given to tubes on either side of the "2" in which there was rather less and rather more haemolysis respectively than in tube 2. In this way the figures 4, 3, 2, 1 or 0 were allotted to each tube, 2, 4 or more in number according to the dilutions of serum employed, each with 3 and 5 units of complement. If all 4 tubes in a test failed to give haemolysis in any tube, the result would read 4-4-4-4 (abbreviated as 4 × 4) and would be called a *strong positive*; if there were complete haemolysis in all 4 tubes, 0 0 0 0 (abbreviated 0 × 0), the reading would be *quite negative*. 4-4-3-1, 3-2-1-0 and 2-1-0.0. would be intermediate readings and would be called positive and weak positive (or doubtful, according to official notation). The tubes reading from left to right would contain 1 in 15 serum dilution and 5 units complement, 1 in 15 serum and 3 units complement, 1 in 30 serum and 5 units complement, 1 in 30 serum and 3 units complement, or with higher dilutions of serum 1 in 60, 1 in 120 and so on, each with 5 and 3 units of complement.

Although in the later years the Harrison Wyler method was employed, I continued to use the old notation for reading the results, partly to maintain the continuity of the records, but mainly because it conveyed to me more information than the recognized "positive," "doubtful" or "negative" would have done. Possibly my predilection for the original nomenclature arose from the fact that from the first I did the Wassermann tests myself and also saw and treated all the patients personally; though later, when both these duties were undertaken by colleagues acting under my direction, more information seemed to be imparted by a numerical notation, especially in patients undergoing treatment (Nabarro, 1927).

The interpretation of the W.R. in children

When interpreting the results of the W.R. in children two groups of cases must be considered, infants and older children. First, it must be emphasized that a W.R., whether it be positive or negative, *is unreliable in infants under the age of 3 months*. A positive result at that age may be due to the maternal antibody which has reached the child transplacentally, in which case it will be gradually eliminated by the child unless the infant, becoming syphilitic later, elaborates its own reagin. Since it is of great importance to the infant's future well-being that treatment be started as soon as possible should the child be syphilitic, a positive W.R. in an infant should be confirmed as follows: The mother's W.R. should be tested if this has not already been done. The infant's blood should be re-tested by a quantitative technique (Faber and Black, 193[illegible]; [illegible] 1938). A

stationary or rising titre would point to the probable syphilitic status of the infant, whereas in the absence of clinical signs of syphilis and a falling titre of the W R. treatment can safely be withheld pending developments. At the same time a confirmatory flocculation test should be performed on the blood. Radiological investigation of the limbs should be made for signs of syphilitic bone changes (Nabarro 1929)

A negative blood in a newborn infant or neonate is similarly inconclusive evidence of the absence of syphilis during the first 3 months of life. On p 199 is given the case of an infant whose W R. was negative at 5½ weeks and positive at 14 weeks with the onset of clinical epiphysitis. In infants over the age of 3 or 4 months *the W R. will be positive in cases of clinical syphilis* in more than 95 per cent of the cases. One does, however come across from time to time an infant whose mother has a positive W R., which itself has signs of congenital syphilis, yet whose W R. is constantly negative. They are difficult to explain, but adults with acquired syphilis may sometimes behave similarly It is conceivable that a child may have had a positive blood reaction for a short time only and that when tested the reaction had become negative. There is no doubt that older children from 3 or 4 years upwards may sometimes give a weakly positive (doubtful ") W R. when examined *routinely* (as I have found on several occasions) *or* because of a suggestive syphilitic manifestation It is my opinion that no matter what the age of the patient may be *a weak positive reaction should always be further investigated* the W R. repeated after a provocative injection, and a careful inquiry made into the personal and family history It is advisable to examine the cerebrospinal fluid of these patients. Doubtful Wassermann reactions may be returned by patients suffering from interstitial keratitis, chronic renal cases, patients who came late under observation with periostitis, Clutton s joints, ulceration of naso-pharynx or other manifestation of late congenital syphilis. The explanation is, I believe, that the infection is weakening either spontaneously or as the result of some—but irregular or insufficient—treatment of the patient The family whose tragic history is recorded on p 40 affords an illuminating example of weak serological reactions in mother and children being overlooked of not going sufficiently deeply into the family history so that the disease which had stricken the family was not discovered before it had wrought all the mischief it did and of an unfortunate lack of co-operation between the various hospitals and other institutions concerne at which the different members of the family attended. In my experi ence of this disease such a lack of co-operation was by no means a isolated instance.

Alternating positive and negative reactions

As sometimes occurs in acquired syphilis in adults, so also in congenita syphilis in children one comes across cases in which a positive and nega

tive reaction alternate. Many years ago Dr Golla then of the Maudsley Mental Hospital, London, wrote to me saying that in examining the blood of mentally-defective children he frequently came across cases in which the W R. fluctuated in patients *apparently free from the suspicion of a syphilitic taint* Among older children and adult defectives such cases, he said, did not occur Could I suggest any explanation to him or were such apparently fortuitous variations of the W R. at all common in quite young children? We were obviously not dealing here with false positive reactions (to be described shortly) but with alternating reactions, and my experience was that they were most likely to occur in children in whom one or other parent had a positive W R. or a syphilitic history and that the *patient a mental defect was probably due in such a case to a syphili*tic agenesis or maldevelopment of the brain In several instances of an ageing infection in a family especially in the father we came across patients with alternating W R. s. Anomalous blood serological reactions were sometimes given by children whose mother was herself a congenital syphilitic, and in one case by the daughter of a man with congenital tabes dorsalis, though the girl had no syphilitic symptoms.

Reversal of the Serum Tests

As a rule it is found that the younger a patient comes under treatment the sooner will the serum tests become negative. In a few infants one has seen a negative W R. follow *a single course* of sulpharsphenamine, though one was not usually content with such a minimal amount of treatment. It would certainly have been followed by a serological and/or clinical relapse after a shorter or longer interval. Bismuth was found equally useful in treatment, for we had several infants whose blood and spinal fluid reactions were strongly positive (4 × 4), but became negative (0 × 0) in both blood and spinal fluid after one course of bismyl injections.

In older patients, those with interstitial keratitis, periostitis perforation of the palate or other lesion of late congenital syphilis, the W R. might not show signs of ultimate reversal until after several years treatment, and even then the blood might take 12, 18 or 24 months to become finally negative. Moreover some of these patients had unstable negatives which relapsed again, albeit temporarily some years later (See also Beerman, 1936)

Relapse of serological reactions

We found, particularly in the earlier years of running the clinic that serological relapses occasionally occurred. These were sometimes accompanied by clinical relapse. We found that relapses occurred in cases in which treatment had been irregular or insufficient When the blood serology is found to have relapsed, it is wise to examine the cerebrospinal fluid, because sometimes one finds the fluid positive, which would require

the appropriate treatment—penicillin tryparsamide, pyretotherapy—as described under neurosyphilis.

Tests of cure

It is a counsel of perfection, to recommend that all congenital syphilitic patients, before being finally declared cured should have been free from symptoms and have had negative serological tests for at least 5 years and, as a final test of cure, should be given a provocative injection of neo-arsphenamine one week before a lumbar puncture is performed and Wassermann tests of the blood and spinal fluid are carried out.

False-positive reactions

By a false positive reactor is meant an individual other than a syphilis-infected person in whom a positive serological reaction is obtained (*Lancet*, Annotn. 1952). During the past 20 years relatively large masses of people have been subjected to serological tests, blood-donors, expectant mothers, and, additionally in America, the armed forces and in certain States, candidates for marriage. A certain proportion of these have been found with a positive W R and or flocculation test, and the question has arisen as to the meaning of these reactors Some are treated syphilitics, others latent congenital or acquired syphilitics, as may be ascertained by careful inquiry whereas others may be non-syphilitic or biological false positive reactors. Various writers collectively give a long list of diseases in which false-positive reactions have been obtained. Apart from yaws, bejel and other treponematoses and relapsing fever (a spirochaetosis) upper respiratory tract infections, virus pneumonia, vaccination against small pox, and various dermatoses have all been credited with being the cause of false positives. It is important to bear in mind the fact that certain skin conditions such as psoriasis, pityriasis rosea, scleroderma and erythema iris may give partial positive (so-called doubtful) reactions. Should the technique employed be too sensitive it is possible for a strong positive reaction to be returned, as I once saw in a case about which my opinion wa ught. Gargoylism is another condition in which a weak or even ly positive W R may be returned, as I have seen on three o e probability that the disease is due to disorder of lipoid metab explains the false positive reaction obtained in f t) p 351). Generally speaking a false positive a few weeks or months, but it may be chronic be hoped that the treponema immobilizati by Nelson and his colleagues and confirme (1953) will enable investigators to separate the non-syphilitic.

Finally since the following points cannot or too often repeated

(1) The importance to the rising generation of doing adequate antenatal testing of *all* expectant mothers—and here it is important to refer to mothers attended by some general practitioners and by midwives who may escape the net of antenatal testing

(2) The importance of testing *all* the members of a family in which one member has been found positive and of treating such an individual if still under or at a child bearing age.[1]

(3) The importance of examining the partner and children of all adults suffering from general paralysis, tabes dorsalis aneurysm and other forms of cardiovascular and tertiary syphilis.

The Examination of the Cerebrospinal Fluid

The cyto-diagnosis of pathological fluids (pleural, meningeal etc) was placed on a firm basis in 1900 by Widal and Ravaut and was applied by them to syphilis in 1902 The examination of the cerebrospinal fluid should be an integral part of the investigation of a presumed case of congenital syphilis of equal importance to the examination of the serum Wassermann reaction. The fluid for examination should be clear and if the first few drops be blood-stained the fluid should be allowed to flow into one tube until it is clear and the remainder collected in a second sterile tube. 5 to 10 ml. of fluid is needed for a complete investigation, but it is not always possible to obtain this amount especially from a small infant. Slight pressure on the jugular veins with the hand round the front of the neck—the Queckenstedt phenomenon—will usually hasten the flow of the fluid. The estimation of the pressure in a crying child is not of much help so we never used a manometer but a note was made of the rate at which the fluid escaped from the needle A fine needle was always used for the lumbar puncture since this was less likely to give rise to post-puncture leakage and headache The tube with fluid was removed before the needle was withdrawn from the spine lest a drop of blood which occasionally escapes with the withdrawal of the needle should contaminate the clear fluid in the tube A fluid which is obviously blood-stained is useless for examination and a week should be allowed to elapse before the lumbar puncture is repeated The macroscopic appearance of the fluid is described in the chapter on neurosyphilis (p. [illegible]5)

1 Cell count It is recommended to do the cell count with a [illegible] blood-counting pipette diluting the fluid 10 times with [illegible] coloured with methyl violet The cell count should be done soon after the fluid is withdrawn and after shaking the tube to distribute the [illegible] evenly The counting is usually done by using a [illegible] chamber The normal number is variously given by [illegible]

[1] Leading article in *Lancet* [illegible]

from 0 to 10 per c. mm In common with many observers I have regarded 5 cells per c. mm as the upper limit of normality

My method of doing the cell count, though probably not so accurate as a direct count, was tested on several occasions against the pipette method and found to be in close agreement with it so that the time saved was a worthwhile consideration. A measured volume of the cerebrospinal fluid (5 to 10 ml according to the amount available) was centrifuged at 2 000 r p m. for 5 minutes and as much of the fluid poured off as would come by inverting the centrifugal tube. The residual fluid left in the tube was then thoroughly mixed with a standard platinum loop and 3 loopfuls of the sediment and 3 loopfuls of diluent (acetic acid 1 5 per cent coloured with methyl violet) thoroughly mixed on an ordinary slide and covered with an ordinary coverslip The number of cells counted in 10 fields, using a $\frac{1}{6}$-in. objective and a No 2 eyepiece, gave the number of cells present in 1 ml. of fluid. If less than 10 ml of fluid was examined the requisite adjustment was made.

In neurosyphilis the cells are nearly always small lymphocytes, with a small admixture of large mononuclear endothelial and plasma cells. In the more acute cases some polymorphonuclears may be present—rarely in our experience exceeding 20 per cent of the total cell count. The various tables of spinal fluids (see pp 277–279) show the number of cells present in our cases and we found that, on the whole, the cells were fewer in number than in adult cases, particularly adult paretics

2 *Total protein* The normal protein in the cerebrospinal fluid varies from 10 to 30 mg per 100 ml. of fluid. We usually estimated the total protein by the Aufrecht albuminometer in which a modified Esbach reagent was added to the fluid (each in a fixed quantity marked on the tube), the tube inverted a few times and centrifuged at 2 000 revolutions for 2–3 minutes. The tube was graduated in percentages of protein, but we found the results obtained by this method rather below those yielded by the diaphanometric method of Mestrezat. As a rule the total protein was rarely above 0 1 per cent, though occasionally a figure as high as 0·4 per cent was obtained. Dattner recommends an electro-photometric apparatus, sulphosalicylic acid being used as the precipitating agent. He insists that it is very important that the cell count and the protein estimation be carefully done.

For the globulin estimation we always used the Nonne-Apelt method (N.A.), which consists of the slow addition down the side of the test tube of 1 ml. of a saturated solution of ammonium sulphate to an equal volume of the cerebrospinal fluid After standing for a minute or two a precipitation at the line of contact indicates increase of globulin the numbers 1 to 5 indicating the degrees of precipitation due to increased amounts of globulin present. The tube may later be lightly shaken when the varying turbidity will also indicate the amount of globulin present

3 *The colloidal gold reaction* (Lange) This reaction is dependent upon the precipitation by the globulins in the spinal fluid of the gold sol, even in the presence of albumins which tend to protect the sol. The preparation of the colloidal gold solution was always difficult, for one could never be certain that the sol was of just the right sensitivity until it was tested with a positive and negative control. Once this had been ascertained, the actual test was easy of application and the change in colour of the spinal fluid plus reagent from the normal pale red through the reddish blue, purple, pale blue to colourless represented different degrees of precipitation of the gold in the sol. These were formerly and throughout my observations, represented by the numerals 0 to 5 the colourless completely precipitated tube being called 5 pale blue 4, purple 3 reddish blue 2 and pale red-blue 1 Ten tubes were used with gradually diminishing volumes of fluid, and the numbers representing the colour of the contents, for example 555 554,3210 would be called a Lange curve With the five decolorized tubes (rated at 5 each) at the head of this curve, we have the paretic type of curve. Other spinal fluids may show a luetic curve with higher figures in the middle of the curve and rarely a 5 for example 1123421000 others, only the figures 0 1 and 2. Owing to the difficulty mentioned in preparing gold solutions which were dependable from one batch to another other colloidal substances such as benzoin and mastic were prepared. We tried both these substances for a time together with the gold sol, but they were not found satisfactory Lange and Harris (1945) reported upon a really dependable gold sol and suggested a different nomenclature from the Lange curve formerly used. Complete discoloration of the contents of a tube receives 18 to 20 points, so that a paretic fluid showing seven or eight decolorized tubes would receive 126 to 160 points for those tubes plus perhaps 20 or more points for the last two tubes The highest score possible is 180 to 200 points, and the gradual improvement usually observed in the fluid as the result of treatment would be reflected in the reduction in the total number of points scored.

At one time I thought, as other observers had done, that the paretic type of curve could be relied upon for the diagnosis of general paresis in young children, and that when this type of curve occurred the children could be kept alive for only a few years in the absence of any treatment. With appropriate treatment, however we succeeded in keeping such patients alive for several years—even up to 30 or more—but since their intellect never developed *pari passu* with their physical growth, our interference now seems to have been unjustified. We noted also that high figures in the Lange curve occurred in patients who subsequently showed signs of severe involvement of the central nervous system, often with marked cerebral degeneration consequent upon meningovascular syphilis. On the other hand one has at times met with Lange curves showing only the low figures of 1 or 2, but in the absence of other evidence of

neurosyphilis such as increased cells and/or protein these low figure curves have been discounted.

4. *The complement fixation test Wassermann reaction* This is by most authorities regarded as the final arbiter of the presence of neurosyphilis. The three previous tests of the cerebrospinal fluid may be positive in a non syphilitic case, but a positive W R. in addition to one or more positive results with the other tests, is conclusive evidence of neurosyphilis, except possibly in the rare event of an acute bacterial meningitis occurring in a syphilitic child in whom there may be a leakage of the blood reagin into the inflammatory spinal fluid.

The reagin in the cerebrospinal fluid is often considerably smaller in amount than in the blood so correspondingly larger volumes of fluid should be used for the test. The amounts of fluid we usually employed in carrying out the test were 0·1 0·2, 0 5 and 0·8 ml. and a fluid was never reported as giving a negative W R unless one had used 0·8 ml., a cholesterinized antigen and 3 units of complement. As in the case of blood serum, the amount of haemolysis produced in the test tubes may be represented by the figures 4, 3 2 1 and 0 and a fluid giving a reading of 4.4.4.4. (4 × 4) with all the tubes (0·1 0·2 0·5 and 0·8 ml of fluid) would be called very strongly positive. A fluid which was improving as the result of treatment would be reported for example as progressively 4.4.2 1 3 2 1 0 and finally 0 0,0 0 (or 0 × 0).

It has been said that a positive serological reaction in the spinal fluid may be found in association with a negative W R. in the blood, a phenomenon which is by no means uncommon in acquired tabes dorsalis. During the whole of our experience with *congenital* syphilis, however we have only once come across this combination in an untreated patient (see p 277)

According to most authorities (Jeans and Cooke and many others), a fluid should not be regarded as coming from a case of neurosyphilis unless the W R was positive others such as Kalz Friedman Schenker and Fischer (1946) are of the opinion that a moderately strong W R in the cerebrospinal fluid of *newborn* syphilitic infants in the absence of any confirmatory evidence, such as increase of cells or of protein should not be regarded as proof of neurosyphilis they consider such a result may be due to permeation or passive transfer of reagin from the blood into the spinal fluid. We are unable to express an opinion upon this point, since we had little opportunity to examine the spinal fluid of neonates, but in our considerable experience of spinal fluid investigations of rather older infants—from 2 months upwards—we did not encounter a single case in which a Type 1 fluid in which the W R was negative (see p. 274), subsequently became a Type 2 or 3 fluid with a positive W R On the other hand, we had at least 8 patients, among the 640 whose spinal fluids we examined in whom the fluids relapsed (W R cells, etc.) after having

become negative. There was usually a synchronous relapse of the blood W. R. in these cases. In the end we were nearly always able to render the spinal fluid negative, but owing to our inability to follow up our cases as the result of the war and the disbanding of the Venereal Diseases Clinic at Great Ormond Street we are unfortunately unaware of the after history of these patients.

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CHAPTER 6

THE CLINICAL PICTURE

In the past most authorities grouped the symptoms of congenital syphilis under two headings, early and late. Findlay it is true, talked of intermediate symptoms in which were included eczema oris and condyloma, but expressed doubt as to the justification for so doing Jeans and Cooke describe the types of early skin lesions and mention that late secondary lesions of the skin and mucous membranes may occur during the latter part of the first or the early part of the second year—the so-called late secondaries or recurrences. From my experience at Great Ormond Street during the course of this study based on records of nearly 900 syphilitic families, I ventured to suggest the classification of the offspring of these families given in Chapter 1 The *neonatal* and *early infantile* types of congenital syphilis were the most striking at the beginning of the present century and during the first world war and it is those types which will be described here, though it must be emphasized that at the present day they are distinctly rare in this country A notable diminution in incidence has accompanied the decline in the intensity of the disease.

The older writers were very concerned about the date of appearance of the symptoms in making the diagnosis of congenital syphilis and particularly as to when a mother who wished to act as a wet nurse could be declared free from syphilis. Still states that his experience, like that of others, was that the appearance of symptoms in a syphilitic child was "seldom delayed beyond the end of the second month and that it was rare for the first evidence to occur later than the end of the third month." Now that we have the Wassermann reaction and the X ray appearances of the infant's limbs to help in making the diagnosis, the date of appearance of the symptoms is rather of academic interest than of practical importance.

The gradual evolution of the views of British clinicians and pathologists can be learnt from four symposia which have been held in London at different times upon the subject. The first, in 1876, was held at the Pathological Society of London, at which the discussion was opened by Sir Jonathan Hutchinson and was continued by the foremost clinicians of the day During the discussion Sir Samuel Wilks remarked there is not a disease like syphilis in our nosology" The full report of the symposium occupies no less than 125 pages of the *Transactions* of the Pathological Society It was more than 30 years later during which time the importance of congenital syphilis had become increasingly

recognized that the second symposium was held, in 1908 at the Society for the Study of Disease in Childhood, with Mr Clement Lucas in the Chair Many noted paediatricians of the day discussed the various lesions and clinical manifestations of infantile congenital syphilis and their contributions to the discussion are duly recorded in the *British Journal of Children's Diseases*. The third symposium was held at the Royal Society of Medicine in 1912, when the Society for the Study of Disease in Childhood had been merged with the Children's Section of the Royal Society of Medicine. Sir Henry Morris presided. Various aspects of syphilis were discussed and among the speakers was Sir Frederick Mott, who confined his contribution to congenital syphilis and its relation to the public health. The report of the symposium occupies nearly 200 pages of the proceedings of the society The fourth symposium was held in 1920 after the first world war when the incidence of congenital and adult acquired syphilis had markedly increased, again at the Royal Society of Medicine. Sir Humphry Rolleston presided Sir Frederick Mott again spoke and many paediatricians and others interested in syphilitic specialties (eyes, teeth, etc.) contributed to the discussion

It is by studying the reports of these symposia that one is able to learn what were the views of specialists at those particular epochs and special attention should be drawn to the changes which have taken place in the various aspects of congenital syphilis—symptomatology mode of transmission, and, above all, the prevention and treatment of the disease—since the date of the Fourth British Symposium in 1920.

Before describing in detail the individual symptoms, it will be convenient to give a general account of the disease as it appeared to the practitioners of a generation ago Still's admirable résumé forms the basis of the account which follows. *The syphilitic infant usually presents a healthy* appearance at birth and for some weeks afterwards. Then its breathing becomes snuffling owing to rhinitis and at about the same time a rash appears in the ano-genital region and on the face, more rarely on the trunk and limbs. The cry is peculiarly hoarse, as if the child were suffering from some form of laryngitis The spleen is usually somewhat enlarged, the liver and lymphatic glands less frequently so and the testicles occasionally so The limbs may become tender on handling owing to syphilitic osteochondritis and from the same cause there may be a disinclination or an actual inability to move one or more of the limbs—the so-called Parrot's pseudo-paralysis. The infant soon shows the toxic effects of the infection—loss of weight dryness and earthy discoloration of the skin, with sometimes marked wasting so that the infant comes to acquire the old man look, so aptly described by Doublet as la miniature de la décrépitude." Other symptoms observable during the first trimester include nephritis, ascites from peritonitis, eye lesions (choroido-retinitis and iritis), dactylitis and inflammation of the nails

Two interesting case histories may be given here. A female infant, 4 months old, was sent to Great Ormond Street by her doctor whose accompanying letter said "This baby has abdominal distension. Is it a megacolon? Would you do a colotomy? It is steadily increasing The child was breast-fed for two

months but was then taken off the breast as she was not getting on. There was no vomiting and the child passed good-size motions. The letter continued "She has had abdominal massage enemas and liquid paraffin for weeks but there is no improvement." On examination at the hospital she was described as a healthy looking child, whose abdomen was very distended so that the liver and spleen could not be felt. The abdomen was very rigid, especially in the right hypochondrium. She was admitted to the ward under the care of Dr (later Sir) Robert Hutchison. The child had a coarse vertical nystagmus but no abnormality was seen in the fundi (P G Doyne) and the C.S F was normal, though the blood W R. was strongly positive. This case is referred to again in Table 16, No. 14, for her C.S.F became positive later and subsequently relapsed, and the mother was herself congenitally syphilitic.

The other case of abdominal distension occurred in a premature (8 months) baby whose birth-weight was only 3 lb. 14 oz. (1 757 G). During the first weeks of life the infant is said to have been healthy and to have slept well. At about 2 months of age the abdomen was distended, which the doctor attributed to overfeeding, so her feed was cut down to 1½ drams (2·6 G) Cow and Gate dried milk in 2 oz. (56·7 ml.) of water 3 or 4 times a day for 3 weeks before the infant was admitted to hospital. There was no rash or snuffles, the abdomen was distended owing to considerable enlargement of liver and spleen, but no free fluid could be demonstrated. There was bleeding from the gums. The child died at about 3 months and post mortem many lesions characteristic of congenital syphilis were present, also hypertrophy and ulceration of the rectal mucous membrane (see p 164).

Towards the end of the first year in the absence of efficient treatment the patient may exhibit varying degrees of anaemia Parrot's nodes may be seen and felt as bony thickenings of the bones surrounding the anterior fontanelle or the skull bones may show evidence of necrosis or of craniotabes. Hydrocephalus, convulsions and other manifestations of cerebrospinal involvement are apt to be present at this stage As a result of the snuffles there may be varying degrees of depression of the bridge of the nose and as sometimes happens in the acquired disease there may be loss of hair in some cases of congenital syphilis though in others the hair may be unduly thick.

The deciduous teeth may be markedly hypoplastic and exhibit a proneness to early decay The permanent teeth in a considerable number of cases show the characteristic features of the Hutchinsonian incisors—hypoplasia, peg-shape and with a central notch in the narrowed cutting edge—and the dome shaped or the mulberry types of 6 year-old molars (Moon's molars)

If the disease has not been recognized or has been insufficiently treated in infancy and early childhood the symptoms of late congenital syphilis may manifest themselves at any time after the third year—even as late as the fourth or fifth decade of life The commonest lesion of late congenital syphilis is interstitial keratitis which may be associated with nerve-deafness and Hutchinsonian teeth the three manifestations constituting the Hutchinsonian triad The tibiae may be characteristically affected by

a diffuse and chronic periostitis gummata may occur in the skin, liver or the bones and particularly in the bones of the nose and palate. Chronic synovitis with effusion into the knee joints may occur and more rarely cases of osteo-arthritis with gross changes in the articular surfaces. Meningovascular changes in a considerable number of imperfectly-treated cases of congenital syphilis lead to meningo-encephalo-myelitis and eventually to juvenile general paralysis and juvenile tabes. Haemoglobinuria lymph-node enlargement and certain endocrine disturbances may occur at this stage.

The mere recital of the possible symptoms of congenital syphilis is sufficient to show what a good imitator of other clinico-pathological conditions the disease can be, but it must not be assumed that patients suffer from all or even many of the symptoms mentioned. Often there is only one symptom of active disease, for example, keratitis or periostitis, but on investigation several other stigmata, such as old iritis or choroido-*retinitis rhagades or Hutchinsonian teeth may be found* *The tendency* for certain tissues or organs of the members of a family to be vulnerable to the treponema of syphilis seems to be a noticeable feature of the disease to which several observers have drawn attention. Fuller consideration of this aspect of the disease is given later (Chapter 10), and after this general preamble it remains to describe in detail how the various organs and tissues may react to the syphilitic virus.

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CHAPTER 7

SYMPTOMATOLOGY

CUTANEOUS MANIFESTATIONS

It is rare for syphilitic infants to be born alive and with active signs and symptoms of the disease upon them. When this does occur the infants are wasted and wizened, often resembling a monkey rather than a human being. The skin is harsh and wrinkled all over the body with varying types of eruption in different situations. Frequently this early eruption is bullous in character—*syphilitic pemphigus* (Fig 20)—which in mild



Fig 20 Syphilitic pemphigus in a child of 4 weeks
(*Courtesy of Prof Engel*)

cases presents bullae on the limbs and possibly on the face, but in severe cases also on the body Ballantyne explains this frequent manifestation of foetal and neonatal syphilis in the loose attachment of the epidermis to the underlying skin at this period of life, and in the resulting tendency to desquamation." The contents of the bullae may be clear or blood stained and later become turbid or even purulent. Many treponemata may be present in this fluid A pemphigus present at birth is always syphilitic, but one arising a few days after birth may be a *pemphigus neonatorum* due to pyogenic cocci which can be demonstrated in the contents

of the blebs. Another diagnostic feature is that syphilitic pemphigus is always present on the palms and soles, whereas pemphigus neonatorum, should it attack the hands and feet, does so at a late stage. Furthermore, in syphilitic cases other types of rash—erythematous, macular papular—may be present, especially around the mouth and in the ano-genital region. The infant is usually pot bellied which is due to the presence of an enlarged liver and spleen, accompanied not infrequently by free fluid in the abdominal cavity The characteristic snuffles and peculiar hoarse



FIG 21 Typical lesions around the mouth of a syphilitic infant 3 months old whose father died of congenital general paralysis

cry the result of rhinitis and laryngitis, with haemorrhages *from* the deeply-excoriated lips, nose and anal region will probably also be present These infants are overwhelmed by the intensity of their infection and practically all die within a few days, certainly within a few weeks. Such severe infections are practically never seen in this country nowadays, though they were not uncommon after the first world war and doubtless are to be seen to-day among under-developed peoples in all localities, for example, Indonesia (Prof Rosenheim) Malaya (Dr Elaine Field) (*personal communications*)

As stated above in the great majority of cases an infant who subsequently shows evidence of congenital syphilis looks quite healthy at birth and may frequently be described as a bonny baby with a birth-weight of 7 or even more pounds. After a variable time, it may be only 2 or 3 weeks or it may in rare cases be as long as 10 to 12 weeks, the infant fails to thrive and the characteristic manifestations of the disease become apparent. The two commonest symptoms are rash and rhinitis which occur in from 70 to 95 per cent of the cases. The rhinitis produces snuffling respiration or "snuffles," the symptom most commonly associated with congenital syphilis. It is often difficult to elicit from the mother which appeared first, the



Fig. 22. Severe facial lesions in a 4-months-old infant
(*Courtesy of Prof. Engel.*)



Fig. 23 A maculo-papular eruption of congenital syphilis in a 2-months-old infant (*Courtesy of Prof. Engel.*)

rash or the snuffles, because the interval between the dates of their appearance may be a matter of a few days only and in any event the order of appearance is of academic interest only Of more importance is the fact that both the rash and snuffles may be so mild in degree and of such short duration that the disease is not suspected at the time and it may remain latent for years, to reappear in the form of *lues congenita tarda.*

The commonest type of skin lesion seen in these very young children is a maculo-roseolar or maculo-papular eruption which closely resembles the rash seen in the secondary stage of the acquired disease (Figs. 21–23) It is varied in character exhibiting erythematous, macular papular and scaly lesions which may be co-existent in different regions of the body The first parts to be affected are the lower portion of the trunk and flexor surfaces of the legs. *Shortly afterwards the rash appears on the face and,*

as was pointed out by Still, its distribution here is peculiar if the face be considered as divided into thirds by vertical divisions, the middle third is the part specially affected by the syphilitic rash. A rash limited almost entirely to the chin the upper lip the inner ends of the supra-orbital ridges and just above the bridge of the nose, is strongly suggestive of syphilis. In situations where the skin is constantly moist, such as the buttocks and genitalia the eruption becomes almost confluent and eczematoid in character and presents a somewhat characteristic glazed appearance. Around the orifices the mouth, nostrils and anus, the tissues are often infiltrated and the lesions become excoriated and are frequently deeply fissured and haemorrhagic, so that when healed they give rise to radiating scars known as rhagades. These are a distinctive stigma of congenital syphilis in later life. It should be emphasized that to be diagnostic of syphilis the scars should be linear and radiating upwards and outwards from the side of the upper lip and downwards in the case of the lower lip. This is well shown in Fig 24 The irregular scarring sometimes seen at the angles of the mouth in children or adults after a severe illness and scars on the lips resulting from some antecedent injury must not be mistaken for the rhagades of congenital syphilis. The rash has a characteristic reddish brown or raw ham colour and later takes on a coppery hue. Pigmentation may persist for some time after the rash has cleared. The palms and soles may be indurated and present a dull-red and shiny appearance, but the most characteristic feature in these situations is the peeling which is almost pathognomonic of the disease (Fig 25)



Fig 24. Characteristic scarring around the mouth (rhagades) of a congenitally syphilitic mother This is an important stigma of the disease

It must be borne in mind that the discharges from these lesions often teem with treponemata and every precaution should be taken by nurses and others against acquiring an infection from these babies. Gloves should be worn by nurses when handling them.

Be the rash slight or severe the skin of these infants often exhibits a sallow or earthy tint which has been likened by the French to café au

lat —the French variety with plenty of milk. At times there is definite marasmus, which will be considered in detail later

The hair and the nails are sometimes affected in severe cases. The hair may be brittle and scanty but infantile alopecia, which has been regarded as an important manifestation of congenital syphilis, may certainly be seen in other conditions It was pointed out by Sir Thomas Barlow that thinning of the eyebrows by alopecia in an infant is very suggestive of congenital syphilis. The opposite condition, an abundant crop of dark hair the so-called syphilitic wig or mop has erroneously been



Fig 25 Peeling shiny feet in an infant of 25 days. A similar condition of the palms of the hands was also present The macular eruption seen on the left leg was present over the lower part of the body

regarded as evidence of the disease it may occur in infants who are free from any suspicion of syphilis.

The nails are more often affected than is the hair but *onychia* and *paronychia*, as the inflammation of and around the matrix of the nails is called are not common manifestations of the disease and occur only in severe cases. Several or all of the finger nails, and occasionally also the toe nails may be affected. The inflammation usually starts as a paronychia with reddening and diffuse infiltration of the finger tips, and later spreads to the matrix of the nail (onychia) As a result the nails become narrowed and atrophic and may be shed once or even oftener Occasionally deformity of the nails may persist

Relapses or recurrences of skin lesions which may occur in untreated or inadequately treated infants nearly always assume a form different from

the original eruption. One form is the syphilitic furuncle of Barlow which was stated to occur most commonly on the upper and outer part of the thighs as deep purplish nodules about the size of half a hazel nut. Coutts states they are rare before the ninth month and probably most common at the age of 2 to 3 years. Carpenter whose cases were largely drawn from a slum district of London found that nearly 20 per cent of those showing skin eruptions in congenital syphilis had cutaneous gummata. In his experience they were found chiefly in the first year and more than half the number were seen in the first 6 months of life. They were usually the size of a pea but might be as large as a chestnut or walnut. Possibly the greater incidence and size of the lesions in Carpenter's experience, as compared with that of Coutts, may be associated with the poorer and more neglected condition of the children who attended Carpenter's hospital clinic. Whatever the cause may have been, there is no doubt that the condition has for many years been on the decline, for Still writing in 1908 stated that in his experience such lesions had been very rare, and during the years 1917 to 1939 at Great Ormond Street we saw in all fewer than half a dozen cutaneous gummata in the 900 patients with congenital syphilis who attended the clinic.

We saw no case in children under 1 year of age, the youngest of our patients being a boy who at the age of 1½ years developed an ulcer under the right eye which proved intractable. He had been attending the general outpatients clinic (1925) for a few months before a blood test was taken. This proved to be positive, but after a course of sulpharsphenamine and mercury the ulcer continued to spread. The patient was then seen by Dr (now Sir) Archibald Gray our dermatologist, who thought the irregular ulcerating area scrofulo-dermatous in nature. Cultures yielded mainly streptococci and a few staphylococci, from which a vaccine was prepared and of which four doses were given. This resulted in apparent cure, but two months later the ulcer broke out again and started discharging and it was then thought to be a gumma. Eventually after several courses of "sulfarsenol" injections, hydrarg. c. cret. and sunlight treatment the lesion healed after a duration of 1 year and 10 months, leaving a large scar. The scar remained sound for 2 years, the W. R. and Kahn being negative all the time, and the child defaulted at the age of 5½ years. The nature of the lesion was obscure and its refractoriness to antispecific treatment was a point against its being a gumma. On the other hand, had it been a gumma, the infection with pyogenic cocci might have been responsible for its intractability to treatment. Unfortunately it was not feasible to make diagnostic animal inoculations for either syphilis or tubercle. The case exemplifies the difficulty that may be encountered in actual practice.

Another interesting case of skin-recurrence was that of a girl who attended Dr Frew's clinic in 1923 at the age of 3 months with symptoms of florid congenital syphilis (rash, snuffles and splenomegaly). She was treated with mercury (hydrarg. c. creta and ung. hydrarg.) continuously for 6 months. The W.R. had been negative twice, at 7 and 9 months, and as the child seemed well she was allowed to cease attending and was not followed up. At the age of 2½ years she attended the hospital again, apparently well except for an indolent ulcer around the anus, of which unfortunately no photograph was taken, but

the lesion was described as being gummatous in appearance The W R had become strongly positive and the C.S F was also positive The lesion was obviously a skin-recurrence but for 2 years mercury was still prescribed and the patient s attendance at hospital most unsatisfactory Eventually neo-arsphenamine injections were started at $4^7/_{12}$ years as the mercury was not influencing the W R. though the ulcer had healed. The W R. of the C.S F became negative at the age of 5½ years, but the blood W R. was not negative until the child was 8 years old and had been given bismuth treatment (bismostab and later bisoxyl). This gave rise to marked gingivitis with some destruction of the gum and a well-marked bismuth line With a hydrogen peroxide mouthwash and cessation of all treatment, the child made a good recovery and there was no recurrence of the skin or other lesion when she was last seen at 11 years of age

Condyloma latum

A skin lesion of the late infantile form of the disease is the *condyloma latum* which is to be regarded as a recurrence rather than as a primary eruption. Condylomata usually occur around the anus and on adjoining parts of the genitalia in the form of flat, moist greyish plaques which appear



FIG 26 Mass of condylomata seen at the age of 8 months They had arisen about 2 months earlier Many treponemata were present The lesions cleared in month with sulphostab injections mercury iodide by mouth and a calomel dusting powder (M Eric Lld d patient)

as if stuck to the surface of the skin (Figs 26 27) They are oedematous hypertrophic papules of wart like nature They often occur in groups composed of elements of varying size and at times their surface is actually ulcerated. More rarely they may be found at the angle of the mouth on the lips and eyelids or between the toes

moisture and warmth coexist. In several of our cases where the condylomata were around the anal orifice, the mother complained that the child was suffering from "piles," or that the disease had started as "thrush in the mouth and "passed through" the child to appear as a rash about the anus. The commonest age for condylomata to appear is about the end of the first and during the second year. The youngest case I personally have seen was a child 4 months old who was under the care of my colleague, Dr Sheldon. Still recorded a case as young as 14 days and Findlay came across the condition in a patient 6 weeks old. Of the 31 instances of condyloma recorded in our Great Ormond Street patients, 3 were under 6 months of age, 5 between 7 and 12 months, 19 between 1 and 2 years, 2 between 2 and 3 years, and 1 each at 7 and 8 years. It is of interest to



FIG. 27. Mass of condylomata about the anus of a child aged $1^{8}/_{12}$ years. These were "missed" for 6 months.

note that the incidence of the condition appeared to be waning, for during the 7 years 1917 to 1923 we saw 25 cases, and only 6 cases during the succeeding 12 years to 1935, and no case from 1935 to 1939. The reduced incidence is no doubt due in great measure to the better treatment of infantile congenital syphilis, coupled possibly with the treatment of the mother during pregnancy. As condylomata are of the nature of recurrences their presence in comparatively young infants, as recorded by several observers, may be explained by the assumption that the original skin lesion occurred *in utero*, as Mraček had shown was sometimes the case, and that either spontaneously or as a result of the treatment of the pregnant mother the "early" eruption cleared up before the infant's birth. Sometimes condylomata are apparently the sole manifestation of congenital syphilis and unless the possibility of the disease is borne in mind their true nature may be overlooked. One of our cases was not recog

nized for 6 months by a hospital and a private practitioner another case was missed for 5 months. Diagnosis is really quite simple provided the possibility of congenital syphilis is borne in mind if the surface be lightly scraped and some serum expressed, many treponemata can be found in the expressed fluid either by dark-ground illumination or after staining by Giemsa or Leishman or by the use of Indian ink. Amongst associated lesions we have seen ulceration of the tongue at 1 year ulceration of the lips and gums also at 1 year hydrocephalus, nystagmus and natiform skull at 13 months. In several instances the infants had been treated with mercury for early symptoms and after defaulting had had a clinical relapse in the form of condylomata. Our cases responded well to the ordinary treatment then in vogue, arsenic with mercury iodide or bismuth injections, and the local application of a powder consisting of equal parts of pulv amyli ac bor., zinci oxidi and calomel.

Late skin lesions

Even when the late cutaneous manifestations of congenital syphilis were commoner than they have been in recent times they were always much less frequent than was the early rash of syphilitic infants. Findlay and Watson described an eczematous lesion about the mouth of syphilitic children, radiating towards the cheek. It was red in colour usually dry and scaly but occasionally moist and crusted. The mucous membrane and tissues of the lip might also be affected. The authors regarded the condition as a clinical entity to which they gave the name *eczema oris syphiliticum*. Our experience does not bear out that of Findlay and Watson among several hundred syphilitic patients, although we encountered several cases of dry eczema of the mouth and face which like so many cases of eczema were rather of an intractable nature and apt to relapse, we could hardly regard the lesion as being sufficiently characteristic to merit a specific name Findlay states that this is one of the later manifestations of congenital syphilis, occurring usually after the fourth year of life, but it may be met with during the first and second years, when it is more extensive and severe than when it occurs later We have encountered only few patients who presented late cutaneous manifestations

M.B. born in 1914, snuffled at 5 weeks but had no treatment in infancy Had partial facial palsy since diphtheria. Weak on the legs and ? mentally-defective when first seen at 4 years of age The blood test of patient, as also of her mother and younger sister was strongly positive. Patient was treated during and immediately after the first world war with mercury Arsenical injections were started in 1920, when the blood test was practically negative. At 7 years of age she had an ulcerating lesion on the thigh which was thought to be probably a cutaneous gumma by Dr (now Sir Archibald) Gray notwithstanding the fact that the blood test was negative. Six months later what was assumed to be a condyloma appeared on the vulva, which cleared after one injection of sulfarsenol no treponemata could be found in the scrapings. The child was small

still appeared to be mentally-defective and had constant enuresis. In March 1924, 2½ years after the previous condyloma she developed another one on the vulva and in view of the fact that the W R. had been negative for 4 years, that no treponemata could be found in scrapings and that the enuresis persisted, the diagnosis was changed from *condyloma latum* to *condyloma acuminatum* or Jacquet's erythema (Fig 28). There was no recurrence of the lesion during the ensuing 7 years.

Jacquet's erythema or condyloma acuminatum

Several patients with the vulval lesions of Jacquet's erythema associated with enuresis and an ammoniacal urine were seen at our clinic, who had been sent as being congenital syphilitic. Fig 28 shows such a case

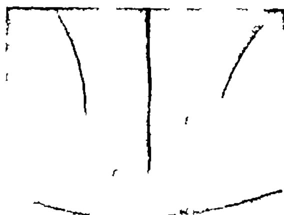


FIG 28 Case of Jacquet's erythema sent to the clinic as a case of syphilitic condyloma. The W R was negative and there was no evidence of syphilis. (Age 5 years)

in which there was no evidence of syphilis and the W R was negative. On treating the urinary condition the lesions clear up satisfactorily

Another patient who after having suffered from slight snuffles, epiphysitis and marasmus in infancy presented as a case of latent congenital syphilis including latent neurosyphilis at the age of 7¹⁰/₁₂ years, improved serologically in both blood and cerebrospinal fluid after a course of malaria and several courses of stabilarsan and bismuth injections. At the age of 11½ years she developed parotitis and 6 months later septic spots on the right leg, one of which was circular and almost "punched out." A cutaneous gumma was the provisional diagnosis, but Dr Gray suggested that the condition might be Bazin's disease. An intradermal Mantoux test was negative, a Dick test slightly positive, but reaction to a streptococcal endotoxin, prepared by Dr Collis in my laboratory was very strongly positive. On oral stovarsol treatment the condition cleared in 3 months.

An adult congenital syphilitic at the age of 50 developed a peculiar condition of the palms of both hands, which were full of cuts and very painful. The

dermatologist at the hospital she was attending diagnosed the lesion as *hyper keratosis palmae* but he found the condition intractable to treatment until having learnt from us that she was a congenital syphilitic, he treated her with bismuth ointment, to which she responded well When the patient was again seen 3 years later her hands had remained well. Although her blood test was negative she was obviously a congenital syphilitic, with a history of eye and knee trouble at about 18 years of age, and she showed typical scars and rhagades round the mouth and chin (see Fig 24).

Phagedenic ulceration of the face resembling lupus has been described as a rare complication of late congenital syphilis by Thomson and by Sequeira (1914) occurring usually between the ages of 8 and 15 years We have had only one similar case, in which a boy of 10 suffered extensive destruction of the skin of the scrotum and groin which resisted ordinary treatment for 6 months. With antisyphilitic treatment and a local mercury dressing the condition was much improved after 4 weeks.

Mucous plaques or patches are a rare manifestation of the late infantile form or the early phase of late congenital syphilis. As these lesions nearly always occur in the mouth, they will be considered with the alimentary system.

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THE RESPIRATORY SYSTEM

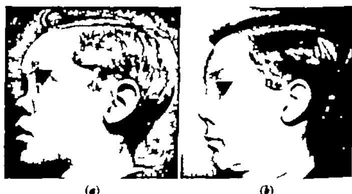
Snuffling breathing— snuffles —is one of the cardinal symptoms and the commonest manifestation of congenital syphilis it must not, however be regarded as pathognomonic of the disease. Still found it present in 70 per cent of his cases, Findlay in 86 per cent, Jeans and Cooke found active rhinitis in 68 per cent and a history of the condition in 3 5 per cent, giving a total of 71 5 per cent. Hochsinger encountered it in 260 out of 263 cases, and was of the opinion that the coryza which is practically always present in congenital syphilis was associated with the peculiar

anatomy and physiology of this part of the respiratory tract at birth and during the neonatal period. Syphilitic rhinitis may be indistinguishable



FIG 29 A woman showing the characteristic facies of congenital syphilis the broad bossed overhanging forehead the sunken bridge to the nose and the haziness of the corneae the result of old interstitial keratitis (Patient of Dr Donald Paterson)

at the outset from rhinitis due to other causes for there may be little associated coryza. Soon however there is a clear mucoid discharge,



(a) (b)

FIG 30 (a) Well-marked saddle-nose in a boy aged 7 years The bridge of the nose had been completely flattened since 3 months of age
(b) After reconstruction of nose by Sir Harold Gillies (age 16½ years)

which quickly becomes thicker and muco-purulent in character With the appearance of the rash on the face and its concomitant exudate, deep fissuring and excoriation around the mouth and nostrils occur so that the

discharge often becomes blood-stained and the parts crusted. Thus may give rise to considerable interference with respiration and the negative pressure thereby induced in the nasal cavities leads to a sucking in of the nasal bones, which may be obvious before the infant is a year old. Even before this occurs, varying degrees of arrested development of the nasal structures may have led to nasal deformities in very young children. The blockage of the anterior nares may also interfere seriously with the child's feeding, which is so important a factor in the paediatric care of these patients.

The rhinitis, which starts as an inflammation of the nasal mucosa may later ulcerate and by downward extension lead to necrosis of the under lying cartilage or bone and even to a perforation of the septum. The ultimate result is the saddle-nose in its several varieties, which formed so marked a feature of congenital syphilis patients until 25 years ago Figs. 29 and 30 show several types of syphilitic nasal deformity the more marked being the result of the destruction of the nasal bones Characteristic foetor ozoena, may accompany the ulceration of the mucous membrane and necrosis of bone and cartilage. The mothers and friends of the patients complain of this symptom more than do the patients themselves. By extension of the inflammatory and ulcerating process and/or by retention of discharge there is not infrequently an otitis media with resulting temporary deafness. Occasionally the inflammation may spread along the duct up to the lachrymal sac, giving rise to epiphora, of which we saw several instances among our clinic patients. A rare sequel to anterior rhinitis, of which we had four examples among our patients, was complete or partial occlusion by scar tissue of one or both nostrils.



FIG 31 Characteristic facies with overhanging "Olympian" forehead in a girl aged $8\frac{1}{2}$ years. The teeth were typically Hutchinsonian and Moon Said to have had meningitis at 9 months and mastoid at 2 years

The peculiar aphonic or hoarse cry of the syphilitic infant is doubtless due to an associated laryngitis in which the vocal cords are involved As happens in the case of rhinitis, the inflammation of the mucous membrane may lead to its ulceration and eventually to necrosis of the cartilage.

An interesting if not unique, observation is recorded by Semon of two brothers, aged $5\frac{1}{2}$ and $3\frac{1}{2}$ years respectively children of a known syphilitic father who died within 3 weeks of each other from acute oedema of the larynx, after having suffered from hoarseness and marked stridor Post mortem, the elder boy showed hyperplasia of all the laryngeal structures, ulceration of the vocal

cords and acute oedema which had given rise to the fatal dyspnoea. In the younger boy who died in spite of a crico-tracheotomy in hospital it was "the middle part of the larynx which was chiefly occluded, owing to acute oedema of the true and false vocal cords, the thyro-arytenoid muscles and the inter arytenoid folds." Shallow ulceration was also present. Semon remarked upon the rarity of deep lesions of the larynx in congenital syphilis. A few weeks later Barlow (1880) reported another case, to which he added the comment that congenital syphilitic disease of the larynx was not so rare as the scanty references to it in the literature might have led one to suppose. He was referring to observations made by an American physician, John Mackenzie, who in the year 1880 published an important paper on "Congenital Syphilis of the Throat based on the study of 150 cases. The cases included patients seen by himself at the throat and children's hospitals of London examples and specimens examined by the invitation of medical friends, and all cases found in the scattered literature. From his investigations Mackenzie concluded that laryngeal disease was by no means rare in congenital syphilis, and that cases were often overlooked in infancy owing to the difficulty in using the laryngoscope and through not examining the larynx carefully at autopsy. At a later age the condition was often called tuberculous. In the same year Ewart exhibited a specimen of "old syphilitic scars in the larynx, trachea and bronchi and stricture of the bronchi leading to chronic disease of the lung in a congenitally-syphilitic woman of 38. Also in 1880 Sturge reported the case of a boy aged 3½ years who had been cured" of his infantile symptoms by mercury rubbings but at the age of one year lost his voice for a time. From this he is said to have "recovered completely" Six months later he again lost his voice and then developed difficulty in breathing. When apparently improving under renewed mercury rubbings, he was "caught by a violent gust of March wind which seemed to take away his breath and he died almost at once on his way to hospital. Post mortem, there was much oedema of the epiglottis and left ary-epiglottic fold extensive ulceration of the vocal cords and extending upwards and downwards, being older and partly cicatrized above.

Carpenter (1901) described the post mortem appearances in two such cases. In one, an infant of 4 months, the ary-epiglottic folds were swollen and an ulcer perforated the thyrohyoid membrane. During life the breathing had been stridulous and the cry aphonic. The second case, a child aged 13 months with chronic snuffles and extensive scarring of the mouth and chin, had "laryngeal whistling audible all over the chest." She was subject to attacks of laryngeal spasm and the mother stated that the child had suffered from "crowing on and off for a long time. The cry was not loud and noisy as it is with healthy vocal cords, but on the contrary dysphonic. The patient died suddenly and at post mortem the epiglottis and ary-epiglottic folds were much swollen. Both vocal cords were ulcerated likewise the ventricular bands." In an infant whose cry was markedly hoarse and who died at the age of 4 months, Still (1908) found slight thickening and roughness of the mucosa over the arytenoid cartilages.

In the author's experience the incidence of laryngeal and throat syphilis has definitely diminished since 1916 doubtless because of the efficacy of the treatment of the disease in infants and young children.

In several of our patients whose cry was aphonic or hoarse in infancy the condition subsided, so presumably the inflammation of the mucous membrane of the larynx underwent resolution. In addition we saw several cases of laryngeal spasm, croup or crowing as the mothers called it.

One patient, born in 1914, was brought to hospital at the age of 3 years on account of difficulty with breathing. She was operated upon for what was thought to be a papilloma of the larynx. She improved for a time, but relapsed about 2 years afterwards, when she nearly died from laryngeal obstruction. On bronchoscopy growths were seen in the region of the vocal cords and after intubation the condition improved temporarily. A blood test was strongly positive for syphilis and two small injections of arsphenamine were given. After the second injection, possibly as the result of a Herxheimer reaction (see p. 429), she had a sudden attack of dyspnoea, for which she was intubated. Three days later during an attempt to re-intubate her the patient died and unfortunately no post-mortem was done and no investigation of the interior of the larynx was made.

Crowing is not necessarily due to laryngeal disease but may be associated with syphilitic disease of the central nervous system, as the case of Peter L. shows (see p. 281).

Four children attending our clinic, at ages ranging from 9 to 10½ years, had hoarse voices unaccompanied by any visible ulceration or other lesion of the palate or nasopharynx. No examination of the larynx was made on these children. Twenty other patients, whose hoarseness was associated with disease of the palate, tonsil and adjacent parts, will be considered under the Alimentary System, (1) The Mouth and Pharynx (page 136).

The lungs in congenital syphilis

In the syphilitic foetus and stillborn infant the lungs are always affected, showing evidence both of retarded and/or abnormal development and of reaction to the causal treponema. The dysplasia affects the bronchi as well as the lung parenchyma. There is considerable overgrowth of bronchial elements, particularly of the mucous membrane, which becomes folded on itself in the interior of dilations or cyst-like formations. The parenchyma of the lung is reduced to a variable number of embryonic alveoli and is permeated by the arborizations of the bronchial tree with its proliferated mucosa, so that the picture presented may be one of an adenoma or sarcoma, the latter on account of the large number of round cells present. The reaction to the treponema takes the form of an interstitial proliferation and of syphilitic vascular lesions (lympharteritis, Clifford Allbutt) which eventuates in varying degrees of fibrosis of the alveoli and the interstitial tissue (interstitial pneumonitis, Fig. 33*b*). The alveolar spaces are filled with desquamated epithelium the cells of which have mostly retained their foetal cuboid shape. These cells undergo fatty and granular degeneration, while the alveolar walls are greatly thickened by a cellular fibrillated connective tissue in which numerous blood vessels, muscular and elastic fibres may be seen (Hutinel 1926). The lungs are increased in volume and consistency and the affected areas

have a greyish white, solid appearance, on account of which Virchow named the condition *pneumonia alba* (Ribbert). Treponemata are to be found in abundance in the alveolar walls and spaces, in the smaller bronchi, and in the walls of the blood vessels. When large areas of both lungs are affected the condition is incompatible with extra uterine life. In infants who have survived birth for some hours or even days the affected parts of the lung are quite airless, which doubtless accounts for some cases of unrecognized congenital syphilis being certified as having died from atelectasis.

Bronchiectasis and congenital syphilis

Hutinel as early as 1905 had written about bronchiectasis in children and his further studies of the subject—clinical and anatomical—led him to believe in the frequency of a syphilitic origin of the condition (1911). This concept, he says, was supported by observations carried out by his own pupils and shortly afterwards Castex and his pupils, on clinical pathological and anatomical grounds, described successively the pulmonary bronchial and pleural lesions of congenital syphilis. At first Hutinel thought only of the part played by congenital syphilis in the causation of fibrosis and bronchiectasis in infants and young children, but subsequently he concluded that the disease might produce similar results in older patients. Fibrosis is common in congenitally-syphilitic patients and is so closely associated with dilation of bronchi that Marfan considered the two processes as forming a single clinical and anatomical entity. Hutinel estimates that congenital syphilis is the causative agent in 50 per cent of cases of bronchiectasis. The lesions may be often limited to one lung or even to only part of a lung particularly the postero-inferior part. The constitutional symptoms of the condition are not very marked or characteristic, and are manifested mainly during acute or subacute attacks. On the other hand local manifestations are more characteristic so also are thoracic deformities with diminished expansion of the chest wall and limited diaphragmatic excursions. These, Hutinel states, are occasioned by the pulmonary fibrosis rather than by the bronchiectasis. The physical signs may be suggestive of pleurisy emphysema and even of cavitation and the commonest error in diagnosis, according to Hutinel, is that of a tuberculous cavity. Fibrosis of the lung is not seen in infancy or early childhood, but much later—in adolescence or adult life. Still (1908) expressed much the same view when he suggested that chronic bronchiectasis and fibroid disease of the lung in children might be a sequel to an early syphilitic lesion which the patient had survived. He emphasized, as did Hutinel, that only one lung or even a part of one lung might be affected by the fibrosis.

While the Continental view of the importance of congenital syphilis in the aetiology of bronchiectasis and pulmonary fibrosis may be an exaggera-

tion, the English and American teaching in two recent text books on diseases of the lungs, which make no mention of congenital syphilis in either condition, appears to me to err in the opposite direction.

The following histories of patients one has treated are of interest in this connection

L.F., born in 1934, had characteristic symptoms of congenital syphilis, with marked ulceration of the lips. He responded well to treatment with sulphostab injections and mercury iodide pills and within a year his symptoms had cleared up and his serological reactions had become persistently negative. At the age of 3½ years he had attacks of vomiting and on examination it was found that the chest was *markedly deformed owing to retraction of the chest wall. He had* enlarged and infected tonsils and adenoids, the right nasal airway was occluded by adhesions between the septum and the turbinate bones the left nostril was almost occluded. These resulted from the early ulceration of the lips which had previously been noted and from the infection of the air passages, which was not so obvious, but which was made manifest by the enlarged and infected tonsils and adenoids and by the cicatrized condition of the air passages observed later These had *led to the retraction of the chest wall, suggesting chronic* bronchiectasis or pulmonary fibrosis. The child died during the war of *H pfifferi* meningitis and no autopsy record was available.

W T born in March 1922 had no infantile symptoms of syphilis but at 7 years of age developed interstitial keratitis of both eyes. For this he was treated at an ophthalmic hospital, being given 8 injections of "stabilarsan (Boots) totalling 0·8 G in 4 months. In November 1930 he started to complain of stiffness and swelling of the right wrist. When admitted to the Children's Hospital in March 1931 it was ascertained that he had complained of cough and pain in the right side of his chest, which it was stated dated from an attack of measles when he was 3 years old. The throat was septic, with tenacious mucopus on the pharyngeal wall. There were some râles and rhonchi over the right lung, the left being clear The teeth showed no anomalies. The fingers were slightly clubbed. The right wrist was fixed with chronic synovitis the left was only slightly stiff X ray examination of the right wrist showed slight rarefaction no erosion of articular surfaces. The report on the chest was much fibrosis at right base, no definite evidence of T.B Left clear The boy's voice was gruff and there were old adhesions of the soft palate to the wall of the pharynx. On laryngoscopic examination the right vocal cord was found to be slightly thickened. The Mantoux test was negative and no tubercle bacilli could be found in the sputum. Despite a positive W R. and the negative results as regards a tuberculous infection, syphilis of the lung was not considered during the 5 weeks the boy was an inpatient. At the special clinic he was treated intensively for 3 years receiving 20 G of arsphenamines, 52 ml. of bisoxyl and mercury iodide pills. At the end of that time the Wassermann reaction had become negative. The wrist remained swollen, but was no longer painful, and the voice remained gruff despite all the treatment the lad had received. After 2 years treatment and when he was about 11 years of age he complained of pain under the heart and in the left side of his chest." The radiologist's report was ? Unresolved pneumonia at left base. The lesions on the right side appear to have cleared entirely " When the patient defaulted at 12 years of age his voice was still gruff and the wrist still swollen. Although one cannot be sure of the diagnosis there seem to be good grounds for believing that the

pulmonary condition was syphilitic and, in the absence of any chest deformity that it was not localized to one side of the chest. (See p. 231.)

The next case was that of a girl, I. P., born in Feb. 1912. As she came to the Children's Hospital, Great Ormond Street, at the age of 8 years, complaining of abdominal symptoms and her liver and spleen were found to be considerably enlarged, only her chest condition will be referred to here, the other symptoms and signs and other details of her case being given on p. 171. On admission to the ward under the care of Sir Robert Hutchison she was very thin and showed distinct stigmata of congenital syphilis, rhagades around the mouth, nose and chin and typical Hutchinsonian teeth. A few lymph-nodes could be felt on both sides of the neck and in the groins. The liver and spleen were both considerably enlarged and there were some enlarged veins over the abdominal and chest walls. There was marked pulsation over the 3rd to the 7th intercostal spaces, most marked in the 3rd, 4th and 5th spaces, over an area roughly between the anterior and mid axillary lines. No pulsation could be seen internal to the nipple line. The left side of the chest moved less than the right on respiration and the left ribs were sucked in on inspiration. On percussion there was an area of wooden dullness all down the left side front and back almost to the mid-line. The heart sounds were forcible, were best heard over the dull area and particularly well in the axilla. There were no murmurs. The breath sounds were much diminished in intensity over the dull area. No fluid was obtained on needling this area. After treatment with drugs (mercury and potassium iodide) and rest in bed the pulsation noted previously was reduced in extent and intensity. At about 9 years of age, as there had not been much response to the oral treatment with mercury and iodide, cautious treatment by injections of neo-arsphenamine was tried, together with the application of mercury ointment to the abdomen. Four courses (27 injections = 7·75 G.) of neo-arsphenamines were given, but they were not well tolerated, as the patient retched or actually vomited after each injection until she was more than half way through the series. Two months after the cessation of treatment, the patient had a mild attack of jaundice which rapidly cleared. The liver remained enlarged as long as the patient was under observation until the age of 17 years. The chest condition gave rise to some anxiety as well as difficulty in diagnosis. The father, an old soldier of the regular army before the first world war, suffered from phthisis for 5 years, from which he died in 1925. For many years previously he had suffered from tabes dorsalis. No sign of active tuberculosis could be found in the daughter's lungs and at 13 years of age the tubercle complement fixation test, which the late Dr. Sévi was investigating in my department at that time, was negative with the human and bovine bacilli. The lung condition was considered to be fibrotic and almost certainly of syphilitic aetiology. three years later, at the age of 16, there was a small haemoptysis, but no sign of active tubercle.

Gummata of the lungs are rare, but cases have been recorded by Barlow (1880), Still (1908) and others. I have come across two cases of pulmonary gummata in infants who died at the age of 4 and 6 weeks respectively, in whom evidence of 'white pneumonia' was also present. Figs. 32 and 33 show the macroscopic and microscopic appearances exhibited by congenitally-syphilitic lungs, which might be mistaken for tuberculous lesions. Giant cells are present but they are not characteristically tuberculous, and treponemata, without tubercle bacilli, were found in suitably stained

sections. There is marked fibrosis of the blood vessels. It should be borne in mind that congenital syphilis and congenital tuberculosis may rarely co-exist in the same patient, but more usually the tuberculous disease in the doubly infected patient is acquired after birth. In a third patient with pulmonary *syphilis, who died at the age of 8 weeks, there* was marked bronchopneumonia but no gummata were seen. The alveoli were filled with exudate, their walls were congested and numerous histiocytes were present. Another syphilitic infant, who died at the age of 4



FIG. 32 Sections of lungs (natural size) from male aged 4 weeks showing several rounded and ovoid gummata, which have a thick rather translucent capsule and a central necrotic zone. The intervening parenchyma show widespread syphilitic bronchopneumonia

weeks, showed general pulmonary consolidation with haemorrhagic areas. Microscopically many macrophages were seen and there was slight fibrosis there was no definite atelectasis and no gummata were visible.

Infantile syphilis predisposes to other infections and it was a well attested observation that many syphilitic infants from 3 to 12 months of age, particularly if untreated or only inadequately treated, succumbed to coccogenic bronchopneumonia.

Somewhat older children may die of syphilitic chronic interstitial pneumonia, as Greenfield (1876) and Carpenter (1901) reported in

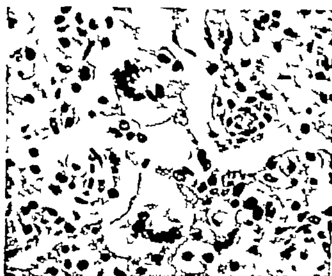


Fig 33 (*a*) Section of the lungs with multiple gummata seen in Fig 32 showing giant-cell formation in an area of syphilitic bronchopneumonia (400)



Fig 33 (*b*) Section of a lung in congenital syphilis infant aged 4 weeks. The alveoli as such are indistinguishable being filled with exudate consisting mainly of inflammatory mononuclear cells and desquamated alveolar cells. These appearances are typical of interstitial pneumonitis (120)

children about 1 year old. In Greenfield's case the lungs were firm and tough, yellowish-white on section and intersected by bands of fibrous tissue. Microscopically there was extreme fibrosis with much fibronuclear proliferation in the septa and walls of the alveoli. In the less marked cases which survive, the fibrosis may spread to the pleura, giving rise to a dry or wet pleurisy and also to the mediastinum in the form of mediastinitis (polyserositis) (Hutinel).

Syphilis and Tuberculosis

"The treponema is not above keeping company with the tubercle bacillus." So wrote Clifford Allbutt in 1921. He, Hutinel and many others have observed that in lung diseases syphilis may be a cause with tuberculosis. In our series of patients about 20 suffered from the double infection. In only a few of these were the lungs the site of the tuberculous lesion and we had no opportunity of observing whether the lesions were more than usually fibrotic or that the blood vessels showed the characteristic syphilitic thickening of their walls.

Judging by the paucity of records of congenital syphilitic disease of the lungs and pulmonary fibrosis, I am of the opinion that the frequency of its occurrence is considerably underestimated but one realizes that in many if not in most, cases it may be impossible to be certain that a fibroid lung has a syphilitic aetiology even if the patient's W R. is found positive, for it is very unlikely that recognizable treponemata would be found in sections of such a lung.

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CARDIOVASCULAR INVOLVEMENT IN CONGENITAL SYPHILIS

There is considerable diversity of opinion among clinicians pathologists and radiologists as to the part played by congenital syphilis in the production of cardiovascular lesions. According to some authorities its rôle is of considerable importance, while others maintain that it is practically negligible. The literature of the subject is fairly extensive and a critical review of 157 relevant papers was published by Josephine Hinrichsen in 1943 In it she points out that the publications reviewed fall into the following main groups

(1) Post mortem findings of (*a*) myocarditis either gross and microscopic or solely the latter (*b*) aortitis, usually without but sometimes associated with aneurysm and (*c*) other vascular lesions.
(2) Clinical records of cardiovascular involvement.
(3) X ray investigations of the heart and aorta.
(4) Studies on the association of maternal or congenital syphilis and congenital morbus cordis, and their possible causal relationship.

Before considering these findings in detail it may be pertinent to make some general observations upon the subject which may help to explain the discordant results and the diversity of opinions recorded by different observers. *Some of the lesions are so widespread* that they are almost incompatible with a post partum existence and are in consequence found only in syphilitic foetuses or in infants who survive birth only a few hours or days. Heavily-infected infants are so ill that a diseased heart may be unsuspected during life and even at autopsy there may be no gross evidence of cardiac syphilis. Warthin (1911) and others have shown that the pathological changes to be described later are not localized to any one area of the heart and that they may be diffuse or so scanty that several pieces of tissue may have to be examined before a diseased area is found. To confirm the nature of the lesion sections must be stained by a special method for the demonstration of the treponema, which may be present in enormous numbers or on the other hand may be very sparse. Warthin stated that treponemata might be localized in the heart when they could not be found elsewhere in the body also that the best results were obtained when tissues were taken within an hour or two of death and immediately fixed in 10 per cent formol for at least 1 and preferably 3 days before being stained for parasites.

That acquired syphilis is a potent cause of cardiovascular disease is generally admitted to be the case, but just how often is one of the unsolved problems of syphilis. McCulloch (1930) states that in untreated cases a conservative estimate is about 25 per cent, lower in well treated

cases. One might therefore expect many congenitally syphilitic children to show signs of heart disease, but as in acquired syphilis the interval between the date of infection and the onset of symptomatic cardiovascular disease is from 15 to 25 years (Carey Coombs 1930 1932) the symptoms and signs of cardiovascular involvement would not as a rule be manifested until late childhood or adolescence. Cases have been reported in the literature to which reference will shortly be made, but their number falls far short of the 25 per cent of all cases of infection given by McCulloch.

The reasons for the apparently lower incidence in congenital as con trasted with acquired, syphilis may be one or more of the following (i) Many congenital syphilitics fail to reach the age of 15 to 25 years and (ii) many of those that do survive will have been efficiently treated. (iii) Dennie and Pakula (1940) make the suggestion that the vascular system of the child may be more resistant to the syphilitic infection than is that of the adult also that even if the aorta is damaged by the treponema, "the reparative index and resiliency of the vascular tissues in children are greater than they are in the adult. (iv) Some of the cases of cardio-aortic disease in young adults ascribed to rheumatism or to acquired syphilis may really have been due to congenital syphilis, any stigmata such as Hutchinson s teeth which may originally have been present having dis-appeared. On the other hand some patients may never exhibit stigmata, yet a careful inquiry into the family history may elicit a specific background such as the father s death from general paralysis or aneurysm, or evidence of congenital syphilis such as old interstitial keratitis in a brother or sister The patient's serum reaction might still be positive, which would help in the diagnosis (though not between congenital and acquired syphilis) or it may have become negative by efflux of time. The sceptics will main-tain that the lesions are due to an acquired and not to the original congeni tal syphilis. While admitting the possibility of reinfection in a congenital specific patient, it is of rare occurrence (Hahn 1941 Allison 1942 Good win and Moore 1946) and to my knowledge I have not come across such a case.

After this digression, we may consider the details of congenital cardio-vascular syphilis as outlined above.

(1) Post mortem findings

(a) Myocarditis. Since von Rosen in 1862 first described a lesion in the heart muscle of a newborn syphilitic infant, many subsequent ob-servers, Kantzow and Virchow[1] (1866), Wendt (1866) Morgan (1868) Coupland (1876), Shattock (1881) and many others have described lesions variously called myxoma, myoma and gumma, in the wall of the heart in a condition of interstitial myocarditis. With the discovery of the treponema

[1] Many of these references will be found in Hinrichsen review

by Schaudinn and Hoffmann in 1905 a great impetus was given to the study of all syphilitic lesions, and Hinrichsen tells us that in the following year 5 authors reported the finding of *T pallidum* in the hearts of syphilitic infants, the reaction to the presence of the parasite varying from case to case.

Warthin (1911) published the first of his series of papers dealing with the pathology and symptomatology of congenital and acquired syphilis. This paper was based on 12 cases of congenital syphilis 9 in infants and young children, and 3 in adolescents, all of which showed cardiac involvement. His conclusions were as follows (1) There exists a special form of interstitial myocarditis localized or diffuse, due to the *T pallidum* and resulting from congenital infection. It may be associated with other lesions of congenital syphilis or *it may be the only demonstrable pathological condition due to congenital syphilis* (2) It is an important cause of asphyxia neonatorum and unexplained sudden death in early life [1] and some of the cases prove that it may cause cardiac weakness in childhood and youth, forming an *anlage* upon which subsequent infections (particularly streptococcal) produce valvular lesions (3) Further the condition may be associated with infantilism, hypoplastic constitution or less severe grades of under-development. (4) Finally it may lead to the production later in life of fibroid heart and coronary sclerosis with the complications and sequelae incident to these conditions." Of the 9 early cases only one had been diagnosed as congenital syphilis the others were all investigated to ascertain the cause of unexplained death. In the case which had been diagnosed as syphilitic, no affection of the heart was suspected although post mortem it showed the most severe interstitial myocarditis with more *T pallidum* than any of the other cases. The 3 older patients, aged respectively 15 18 and 22 years, all had a history of heart disease and were considerably under-developed the girl of 18 showing marked infantilism. The woman of 22 was a blue baby from birth. Death was due to streptococcal endocarditis grafted on an old interstitial myocarditis. The patients father was in the late stages of tabes dorsalis.

In the majority of the early cases the heart was enlarged and dilated, the muscle being uniformly pale or showing lighter areas in the other cases no gross changes were visible and the diseased condition was discovered only on microscopical examination All the older cases showed mitral endocarditis with insufficiency compensatory hypertrophy and dilatation, none of which suggested the syphilitic myocarditis which was seen under the microscope. This consisted in few or many light-staining areas separating or replacing the muscle fibres and composed of fibroblastic or myxomatous tissue which contained numerous lymphocytes, plasma cells and epithelioid cells. Levaditi s stain revealed the treponema

[1] Winogradow stated that sudden death in syphilitic infants might be due to changes in the cardiac ganglia (Hochsinger *loc cit* p 142)

in this fibroblastic tissue, often in incredible numbers. The interstitial process tends to follow the smaller arterioles and capillaries and is abundant also about the medium-sized vessels less so about the larger ones The smaller vessels show an epithelioid proliferation of their walls and Warthin states that obliterative endarteritis was not the common or the most characteristic feature of these congenital cases thus differing from the common variety of cardiac syphilis seen in adults. Marked degenerative changes —a peculiar pale coagulation necrosis—occurs in the heart muscle, so that eventually it is wellnigh impossible to distinguish muscle fibrils from the epithelioid and fibroblastic tissue, and at first sight the appearances might be described as oedema or increase of stroma. The true nature of such soft, cellular semifluid cardiac tumours" variously designated by authors myxoma, myoma, etc., is proved by the presence of many treponemata in them. Giant cells and true gummatous formation were not found in any of these cases and Warthin remarks that the process differs from the gummatous myocarditis seen in late acquired syphilis In some of the newborn the heart muscle showed vacuolated fibres and marked fatty degeneration, the latter contributing to the pale colour and greater translucency of the heart wall. Few parasites were found in these areas of fatty degeneration, which Warthin surmised were not directly due to the toxic action of the treponema but were the result of localized circulatory disturbances. In 1911 Warthin wrote, The relation of syphilis to heart diseases has changed considerably from the view held until comparatively recently and now we read that at least one tenth up to one third or more of all cases of heart disease are due to syphilis. But in this change of view congenital syphilis has not been included and the old teaching still prevails. It is my opinion that modern teaching lays too little stress upon the frequency and importance of cardiac involvement in congenital syphilis.

In later papers Warthin (1912 1914, 1916) records many additional cases mostly in syphilitic infants, in which the lesions resembled those already described cardiovascular syphilis was also recorded in children aged 14 and 18 months and in a congenitally syphilitic man of 25 The last-named came of a definitely syphilitic stock though he himself had enjoyed fair health until his fatal seizure After working hard on a hot day he developed signs of cardiac failure, dyspnoea, cyanosis and pulmonary oedema and succumbed in 3 days The heart was much enlarged and dilated and there was an aneurysmal dilatation of the anterior wall of the ventricle Pale areas were present in the heart muscle, which microscopically showed acute *syphilitic myocarditis* of the whole of the heart wall, with the presence of treponemata Anderson (1915) reported the rupture of the ventricular wall in a 5 year-old girl resulting from syphilitic myocarditis There was definite increase of fibrous tissue, stenosis of the orifices of both coronary arteries and scanty treponemata were present in

the heart muscle. Blacklock and M'Cluskie (1928) reported the case of an infant aged 6 weeks, whose only manifestations of syphilis were in the heart muscle and at the ends of the long bones. There was solution of the cardiac muscle fibres and miliary gummata (syphilomata) in peri vascular spaces and many treponemata in and around the lesions were demonstrated by Jahnel's stain. Stobie (1921), McCulloch (1930) and others mentioned in Hinrichsen's review (and more recently Pratt Thomas (1943)) have reported similar cases of syphilitic myocarditis.

(b) **Aortitis and aneurysm.** Thiry (1898) described lesions in the heart and aorta of a girl aged 13 who had died of juvenile general paralysis, since when many observers have recorded cases of aortitis in syphilitic infants and older children. Melchior (1904) in 3 infants aged 9 days (2) and 5 months, Wiesner (1905) in 9 out of 10 cases of congenital syphilis found changes in the aorta and its main branches and in the pulmonary artery. Later Rach and Bruhns extended and confirmed Wiesner's investigations, whose results were, however, hotly contested by Scharpff (1908). Hinrichsen gives the names of several later observers who have confirmed the presence of aortitis in syphilitic infants, and it would appear that the lesions are more likely to be found in stillborn infants and those who die within a few days than in older children.

When we come to the consideration of aortitis and aneurysm in older children and adults we note similar differences of opinion. Most authorities state that aortitis is rare among congenital syphilitics, yet a number of cases are on record. Turnbull (1915) reported two, one concerned a girl of 17 who suffered from dyspnoea and had a double aortic and an occasional apical presystolic murmur. She died suddenly and at autopsy the left ventricle was dilated and much hypertrophied with aortitis, aortic incompetence and chronic endocarditis. There was a crenated pitted zone in about the first inch of the aorta and the coronary ostia were narrowed. Microscopically the lesions were typical of syphilitic aortitis. The girl's father had died of heart failure at the age of 65 and autopsy revealed aortitis and aortic incompetence. Turnbull's second case occurred in a girl of 7 in whom the ascending and descending aorta presented a number of wrinkled and nodular areas. These showed characteristic syphilitic appearances similar to those seen in the first case but in addition the intima was thickened by an increase in its connective tissue. Warthin (1917) states that should patients survive the less severe manifestations of syphilitic aortitis, the lesions may later heal and give rise to a condition indistinguishable from athero-sclerosis due to any other cause. Klotz (1908) had suggested that these healed lesions of congenital syphilis might give rise to an erroneous diagnosis of *acquired* syphilitic aortitis in the adult. Clifford Allbutt (1921), in an address given in opening a discussion on Visceral Syphilis, refers to a rare case of congenital syphilitic arteritis in a girl of 16 in which the lesion was confined to the abdominal

aorta. Carey Coombs (1930) refers to two cases of syphilitic aortitis in young women of 20 and 25 years of age, both obviously congenital luetics. The former patient also had an abdominal aneurysm and is referred to again later (p 123) the latter had cerebral symptoms and post mortem was found to have a gummatous infiltration at the base of the brain and a typical syphilitic aortitis. McDonald (1934) reported a case of syphilitic aortitis in a boy of 9 who had died from the toxic effects of arsphenamine injections. In addition to the gross and microscopic evidence of syphilitic aortitis, the left ventricle showed cloudy swelling and oedema of its musculature.

From a survey of the literature it seems, says McDonald, that it is by no means rare for specific lesions to be found in the aorta of congenitally syphilitic infants. Microscopically they show the appearances characteristic of acquired mesaortitis in association with *T. pallidum* yet several observers have denied their specificity and state that rheumatic infection of the aorta can simulate the lesions of syphilis. It is possible that the *lesions of foetal or early infantile syphilitic aortitis heal rapidly in most cases* and leave no obvious traces behind, thus resembling tuberculosis but where there is allergy and resistance is low the disease may run an acute course. The bearing of syphilitic allergy on the problem of aortitis in congenital syphilis merits careful consideration and study says McDonald.

Having had his interest in congenital syphilitic aortitis kindled by the occurrence of the case recorded above and by his survey of the literature, McDonald looked for similar cases in the current practice and past records of the Royal Infirmary Newcastle upon Tyne, with the result that in 1934 he was able to report 11 further cases of syphilitic aortitis in patients under 30 years of age. Four of them, males of 21 and 22 and two females of 19 were undoubtedly congenital syphilitics, whereas three males of 24, 29 and 30 and two females of 26 and 30 were *probable* congenital syphilitics. Two others a man of 28 and a woman of 20, may have been congenital syphilitics, but both gave a history of the acquired disease. It is of interest to note that of the 9 undoubted or probable congenitally syphilitic patients, no fewer than 6 were observed in the years 1932–33 when a special look-out was being kept for this type of case. This strongly suggests that if only cardiologists would bear in mind the possibility of cases of cardio-aortic disease in young adults being of congenitally syphilitic origin and made adequate anamnestic investigations, many more such cases would be revealed. It is well known that in acquired syphilis cardio-aortic lesions may be accompanied by pathological conditions of the central nervous system—tabes dorsalis tabo-paresis or general paralysis. So in the congenital form of the disease the association of cardiovascular and cerebrospinal lesions has been reported but what is of greater significance is the fact that *congenital* tabes and general paralysis may first become manifest in the fourth decade of life—I have seen them

start at 35 years of age—so it is presumably equally possible for a *congenital* cardio-aortic disease to manifest itself after the age of 30, when it would be regarded by most observers as being due to acquired syphilis.

An analysis of McDonald's cases brings out the difficulties of diagnosis. In 2 cases a diagnosis of lues tarda was made in 2 others there was a family history of syphilis in a further 2 there was a history of acquired syphilis and in the remaining 5 there was no clinical suspicion of syphilis In only 2 of the cases was a diagnosis of an aortic valvular lesion made, notwithstanding the fact that in the majority of the cases there were gross lesions in the first part of the aorta. In these 2 cases there was definite anatomical evidence of chronic aortic endocarditis. No clinical data were available of 3 cases that were brought in dead. Some degree of coronary occlusion was present in practically all the cases, which makes it seem likely says McDonald, that orthodiagraphy and electrocardiography may be of particular value in establishing a diagnosis. McDonald formulates two conclusions from his observations (1) to exclude syphilitic aortitis before making a clinical diagnosis of rheumatic heart disease in a young adult and (2) to proceed cautiously in the treatment of congenital syphilis with arsenicals, even where there are no obvious indications of aortic disease. It may provoke a Herxheimer reaction, even a fatal one where coronary occlusion exists (Doumer).

Norris (1935), Ward and Sulman (1945) and others have also reported cases of congenital syphilitic aortic disease, but Ward and Sulman state that while such cases undoubtedly occur they are not very common. It is generally admitted that aortitis is common in acquired syphilis then why should it not occur in congenital syphilis they ask. Instead, the sceptics immediately begin to confuse the issue by declaring that the case is due to acquired syphilis possibly extragenital, or that it is due to rheumatic infection. True, it is sometimes difficult to distinguish between these three aetiological factors—acquired syphilis, congenital syphilis and rheumatic infection The age incidence would be rather higher in the syphilitic than in the rheumatic variety The serological reactions may not be helpful for many cases of syphilitic cardiovascular disease give negative complement fixation and flocculation tests, and in the active stage of rheumatic infections the W R. may be positive (Koons and Kissane 1940). The rheumatic heart often, though not invariably shows involvement of the mitral valve along with the aortic dilatation of the aorta favours a syphilitic aetiology Lastly it must be borne in mind that rheumatism and congenital syphilis may coexist in the same patient.

Aggerbeck (1944) reports the interesting case of a girl of 19 whose mother had irregular treatment during her pregnancy so that the patient, although apparently congenitally-syphilitic, had a negative W R. throughout life. She had no serious illnesses until at the age of 19 she developed moderate dyspnoea on exertion, later palpitations but no cardiac pain

she complained also of loss of appetite and lassitude. After a dance she developed acute aortic incompetence and died in about 6 weeks. Post mortem there was marked syphilitic aortitis of the ascending aorta with the characteristic microscopic vascular changes and advanced fatty degeneration and increased connective tissue in the myocardium. The latent period between the time of infection and the onset of aortitis was the usual one of about 20 years.

Even as recently as 1946 Weinberg and Bessinger reported a case of syphilitic gummatous aortitis as a cause of coronary ostial stenosis and myocardial infarction in a white woman of 28 in which the post mortem appearances were confirmatory of syphilis but treponemata could not be demonstrated. In their comment upon the case they remark that most authors emphasize the relatively early age at which syphilitic coronary stenosis may be found, but they make no mention of the point which one has been at pains to stress namely that many of these cases of syphilis are probably *congenital* rather than *acquired*. Undoubtedly many authorities are still unconvinced that congenital syphilis is a cause of aortitis in children and adolescents, and would agree with Hinrichsen that the statement made by Stolkind in 1920 holds good to this day even in view of the cases that have been reported since. Stolkind wrote "So far none of the cases described as congenital syphilitic aortitis in older children, adolescents and adults has been proved ... but although no case had been proved many such cases may exist." In the face of the positive evidence of so many reliable authorities, this viewpoint is in my opinion, indefensible.

Aneurysms are rarities in congenital syphilis. In addition to the few cases referred to in Hinrichsen's review the following may be mentioned a ruptured abdominal aneurysm in a girl of 20 and a thoracic aneurysm in a woman of 48 both being regarded as congenital syphilitics, reported by Coombs (1930) a non pulsatile mediastinal tumour in a congenitally syphilitic girl of 18 which at exploratory operation was opened with fatal result (Dennie and Pakula). One of McDonald's cases, a woman aged 30 had an aneurysm of the aortic arch which on account of haemoptysis and pulmonary symptoms was clinically thought to be a case of pulmonary tuberculosis. At autopsy marked syphilitic aortitis was present, which had eventuated in aneurysm of the aortic arch with rupture into a bronchus. Hutinel (1926) states that Calvin succeeded in collecting about 30 cases of aneurysm in congenital syphilitics.

(c) **Vascular lesions** Whatever view may be held as to the occurrence of aortitis in congenital syphilis patients, there can be no difference of opinion as to frequent occurrence of specific arteritis in the medium sized and smaller arteries of some of these patients. The arteries at the base of the brain are those most commonly affected and there are many such cases on record. Sir Thomas Barlow (1877) reported the case of a female child who died at the age of 10 months after having suffered from

snuffles since early infancy and convulsions up to the age of 4 months choroiditis was also present. In spite of treatment by mercury inunctions the child's condition steadily deteriorated Post mortem there was endarteritis of the meningeal vessels with consequent cerebral changes The same year Barlow recorded the case of a male infant, aged 15 months, with gummata of several cranial nerves associated with extensive syphilitic disease of the vessels of the circle of Willis. These were white, opaque and of almost cartilaginous consistency the lumen was narrowed by thickening of the intima, and cellular infiltration of the muscular and adventitious coats was present. Similar cases have been put on record by Sutherland and Walker and by Chiari in infants aged respectively 16 and 15 months. Carpenter found the arteries in the kidney thickened, chiefly in the media, in a 5 month-old infant who had suffered from syphilitic nephritis. Our own records at Great Ormond Street contain several examples of fibrosis and peri and endarteritis in the vessels of one or more of the viscera as well as instances of marked disease of the cerebral arteries as described by Barlow and others. The changes in the visceral arteries were usually found in infants who died at from 2 to 6 months those with cerebral arterial disease usually died rather later at from 9 to 15 months, with evidence of neurosyphilis (see Chapter 8)

Congenital syphilis is undoubtedly one of the causes of *haemorrhage in the newborn* but it is not of sufficient frequency to justify the designation *syphilis haemorrhagica neonatorum* which has been given to the condition. Wilson, in Philadelphia, among 45 cases of haemorrhage in the newborn found 10 of them syphilitics and of these 6 bled from the umbilicus. Hochsinger is of the opinion that umbilical haemorrhage in syphilitic infants is much more frequently due to disease of the walls of the blood vessels which prevents their efficient contraction, than it is to septic infection. Another possible cause of haemorrhage in congenital syphilis is the reduction of prothrombin in the blood owing to liver disease (Snelling)

Numerous authors have reported the association of Raynaud's phenomenon with congenital syphilis and Hinrichsen mentions in her review that reports of this association were much more numerous from about 1884 to 1907 than they have been since. I did not encounter a marked case of Raynaud's phenomenon among my clinic patients, but some of them suffered from pallor or cyanosis of the fingers and toes after exposure to cold, these attacks being associated with paroxysmal haemoglobinuria On p 397 the occurrence is recorded of Raynaud's phenomenon in sisters who were possibly occult congenital syphilitics (i e having negative W R.) their mother having undoubted congenital lues

It is possible that cases of juvenile generalized arterio-sclerosis, as described by Fremont Smith in a 12 year-old boy originate in the changes described by Rach and Wiesner and others in the adventitia and

media of the medium sized arteries *Enlarged scalp veins* are not infrequently seen in patients suffering from congenital syphilis. The Fourniers regarded them as being syphilitic in origin, but Hochsinger disagrees and states that dilated veins result from hydrocephalic conditions inside the skull Dennie and Pakula think that the thickening and enlargement of these veins are probably due to specific inflammatory changes in their middle coat, since the veins soon return to normal when effective antisyphilitic treatment is given. My own experience has confirmed this observation, but it does not necessarily follow that the veins were diseased antispecific treatment may have relieved the hydrocephalus and by so doing have reduced the size of the veins.

(2) Clinical records of cardiovascular involvement in congenital syphilis

Several authors have reported instances of aortitis and cardiovascular lesions in congenital syphilitic patients who have given no history of any past or present rheumatic manifestation (Roemheld (1912) in a woman of 32 Cummer and Dexter (1912) in a woman of 38 who had tabes dorsalis, syphilitic aortitis and stigmata of congenital syphilis Neugebauer (1914) in a man of 28 and three women of 17 18 and 32, three of these patients being siblings). Findlay states that aortic disease appears to be rarely caused by congenital syphilis in contra-distinction to its frequency in the acquired disease. He records one case in a lad of 15 who complained of breathlessness and praecordial pain and on physical examination revealed an enlarged heart, double aortic murmurs and a Corrigan pulse. He had stigmata of congenital syphilis, a positive Wassermann reaction and gave no history of familial or personal rheumatism.

An important contribution to our knowledge of congenital cardio-aortic syphilis is the paper by Stobie already quoted (see p. 120). Of 18 cases of aortic disease 13 had a syphilitic aetiology two of them aged 21 and 22 years, and possibly a third aged 28 who gave also a history of rheumatism at 21 were almost certainly congenital syphilitics. He refers to Cowan and Fleming's work, in which evidence is adduced suggesting that mitral stenosis and renal fibrosis may in many cases have a common cause, and that cause may in some of the cases be syphilis. Of 15 cases of mitral stenosis studied by Stobie, three had a positive W R. and two of these aged 15 and 31 were almost certainly congenital syphilitics. Of 13 patients with stigmata of congenital lues one, a woman aged 27 had signs and symptoms of aortic disease dyspnoea and pain over the arch of the aorta an aortic systolic murmur and accentuation of the second sound. The W.R. was strongly positive. A brother aged 26 died of tabes dorsalis.

Worster Drought and Danvers-Atkinson (1929) reported the case of a boy of 13 with congenital tabes dorsalis who on auscultation was found to have a mitral systolic and a late diastolic murmur Dennie and Pakula

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heart, diagnosed syphilis in 23 (72 per cent). Various American investigations into this problem appear to favour the conclusion that congenital lues is not an important factor in the causation of heart disease in children (Donaldson 1921 McCulloch 1930, Kooms and Kissane 1940).

In this connection there are two points worthy of note (1) the small proportion of cases of congenital heart disease with a positive W. R. in the United States as compared with Europe and (2) a congenital heart, as Fournier Ballantyne, Still and many others have pointed out may be a manifestation of "dystrophy" the result of syphilis in the mother analogous to the congenital defects which may occur in a foetus following rubella in the mother's early pregnancy In such event the infant would not necessarily be syphilitic, but its congenital defect would none the less be indirectly due to syphilis and, in the absence of a treponemal infection the child's W R. would be negative. It follows, therefore, that in order to obtain a more accurate figure for the association of syphilis with congenital morbus cordis or indeed with any other congenital defect, the mother's blood as well as the child's should be tested as soon as possible and full anamnestic information obtained.

Among our interesting cardiac cases are the following

F S. Born in 1917 Her father contracted syphilis in the first world war for which he was inadequately treated. Her mother died of tuberculosis in 1923 and when the child was brought to hospital little information could be obtained about her early medical history It was thought that in infancy she suffered only from malnutrition. At 8 years of age she had an attack of chorea which is said to have lasted for 10 months and to have led to acute heart failure When admitted to hospital under the care of Dr Poynton her condition was diagnosed as rheumatic carditis, the diagnosis being based upon the history the presence of a systolic thrill and a double mitral murmur On X ray examination the heart was found to be markedly enlarged, with the apex not moving so well as the rest of the ventricle, suggesting the presence of adhesions. A fortnight later rheumatic nodules appeared on both elbows and the right knee Although the child was warded for several months, during which time she was given the orthodox treatment for her rheumatic condition, it was noted that she did not improve. The reason for this was soon to become apparent. About 10 weeks after the rheumatic nodules appeared, the patient developed interstitial keratitis first in the left and a week later in the right eye. A blood test then carried out gave a positive W. R. and the incisor teeth upon more careful inspection were seen to be characteristically Hutchinsonian As her physician considered it inadvisable to give arsenical injections the patient was treated orally with stovarsol. Several months of this treatment produced little if any improvement in her condition so arsenical injections were resorted to During a period of 22 months she received 12.4 G stabilarsan (Boots) and 9 ml bismostab The eyes were rather slow to clear and during treatment a tuberculous abscess appeared under the left side of the mandible the nature of which was confirmed by the finding of tubercle bacilli in the pus. Before the completion of treatment the W R had become negative and it gave 5 subsequent negative results until the patient finally defaulted at 14 years of age When seen by Dr Poynton at 12½ years he reported The patient is much better She has a slight

systolic murmur the presystolic murmur originally present is now gone. When we last saw the girl in the clinic, at the age of 14, she was tall and rather pale the abscess of the neck had healed the left eye was slightly nebulous and she was fit enough to play games at school.

The case is interesting in that three infections—rheumatism, syphilis and tuberculosis—were present, and that until antisyphilitic treatment was given the patient derived no benefit from the recognized treatment for rheumatic carditis.

E.S a girl born in 1925 was brought to the Children's Hospital at 2½ years of age on account of a granulomatous lesion at the angle of her mouth (see Fig 34). She gave no history of infantile symptoms, but the mouth lesion was considered to be luetic and the W R. was found to be strongly positive. The lesion cleared under antisyphilitic treatment, sulphostab 8 G in 40 injections and mercury iodide pills. After 18 months treatment the W.R. was negative and all seemed to be going well, when, at the age of nearly 5 years, a rash appeared on the shins, which Sir Archibald Gray diagnosed as an atypical form of erythema nodosum. At that time the mouth lesion showed no sign of recurrence and the W R was still negative. The year 1932 was a trying one for the patient in January she had diphtheria in April measles in October follicular tonsillitis with joint pains and her doctor discovered a heart lesion. This was confirmed at our hospital by Dr Schlesinger as a rheumatic heart with a diastolic murmur A month later the child complained of pain in the legs and swelling of the right ankle. Clinically she was thought to have periostitis of the tibia, but X rays failed to show anything definite The patient attended the Rheumatism Clinic for a year at the end of which she is stated to have had a systolic murmur only Three months later she was well enough to join the Girl Guides and at 9½ she was discharged from the ordinary medical clinic as being well.

This patient was a treated congenital syphilitic who developed evidence of a rheumatic carditis, with involvement of the mitral valve Progress was satisfactory and when last seen at the age of $11^{10}/_{12}$ there was no evidence of permanent valvular deformity

L.W born in May 1922, had no infantile or later symptoms but was discovered to be a latent congenital syphilitic when 6 years old. He was treated with stabilarsan injections and mercury iodide pills. At 7 years of age the tonsils and adenoids were removed and after a considerable default from his V D. treatment, he developed chorea. He was admitted to a medical ward, as there was some question of a complicating carditis. Nothing definite could be detected in the heart and the chorea gradually subsided and was absent for 9 months. When it recurred the boy complained also of pains in the back and legs. His heart was then found to be enlarged, and systolic and presystolic murmurs were heard in the mitral area. Despite much antisyphilitic treatment the W R. was not quite negative and the blood gave a strong Kahn reaction. During the ensuing 8 months there were periods of further cardiac damage slight haemoptysis for 10 days, enlargement of the liver and oedema of the legs and scrotum. Death occurred at the age of $10^{8}/_{12}$ years. At autopsy there were signs of old rheumatic carditis, pericarditis with adhesions over the anterior surface of the heart dilated right auricle and ventricle and dilated and considerably hypertrophied left ventricle. The endocardium, particularly that of the left ventricle was thickened white and opaque. There was shortening and thickening of the mitral valve with vegetations upon it. In the first part of the arch of the aorta there was a longitudinal linear scar with a depressed base

which was thought by the pathologist to be syphilitic in nature. Unfortunately no sections were cut of this aortic lesion.

This case differs from the preceding one in that the rheumatic manifestations appeared after the patient had received a considerable amount of antisyphilitic treatment and that his cardiac condition deteriorated in spite of further treatment. In fact, it is possible that he was over-treated for he received 19 G. of arsphenamines with mercury iodide over a period of 3½ years.

This patient was a well-treated, possibly over treated, congenital syphilitic who later suffered from chorea and rheumatic pancarditis which proved fatal. The aortic arch presented a scar which was considered to be syphilitic and it is possible that syphilis may have been responsible, with rheumatism, for some of the cardiac manifestations.

L.G., born in 1919, had no definite infantile symptoms of congenital lues but was a "fragile baby." He ailed little until, at the age of 7 4/12 years, he developed *painful* swelling of both knees which his doctor not unnaturally diagnosed as rheumatism. Admitted to hospital some three months later under the care of Dr Poynton, physical examination of the chest revealed "an abrupt, slapping first sound of the heart with a short systolic murmur heard over a small area in the 5th interspace." No definite diagnosis of the cardiac lesion could be made but it was thought to rest between rheumatism and syphilis. No osseous changes were detected in the joints on X-ray examination and a positive W.R. gave evidence of a syphilitic soil. That the joints were cured in less than a year by antisyphilitic treatment appeared to confirm the indubitably syphilitic nature of the arthritis. At the age of 9 years the tonsils and adenoids were enlarged giving rise to cervical adenitis and a discharge from the left ear. Between 10 and 11 years of age he had several fainting attacks and the heart now presented a thrill in addition to a murmur. Dr Poynton's opinion of the heart condition was still the same—rheumatism or syphilis—which, in view of his outstanding experience of rheumatic heart disease in children, is evidence of the difficulty in diagnosis this kind of case may present. During the ensuing 5 years (1931–35) the patient constantly complained of feeling tired, possibly the result of over indulgence in football, cycling and swimming. The cardiac condition continued much the same with a diffuse forcible impulse, a systolic bruit and a pulse rate of 120 per minute. The knees remained quite well and the W.R. had reversed to negative after a year's treatment. When the patient was last seen at the age of 17½ years the blood had given 12 negative serological results. Shortly before the outbreak of war in 1939 his mother wrote saying that the patient was well and that he was following an outdoor occupation. In 1948 contact was again made with the mother who told us that, despite his original cardiac condition, he had joined the Army as an A1 recruit. He had been wounded in the head at Dunkirk and after recovering was placed in category C3 and spent the remaining years of the war in this country. In 1948 he was driving a lorry and still preferred an outdoor life to an indoor occupation. He appeared to be well, she said, apart from being rather pale. It would have been very interesting to have seen him again and to have re-investigated his cardiac condition and arrangements were made to this end, but the patient failed to keep his appointment at the hospital.

This is a difficult and interesting case to interpret. Poynton, with all his experience of heart disease in adults and children, would not commit himself as to the nature of the lesion, whether rheumatic or syphilitic. In the absence of any rheumatic history, such as chorea, one did not regard the painful knees originally complained of as being unequivocal evidence of rheumatism, but in

view of the positive blood test looked upon the joints as well as the cardiac lesion as being possibly of syphilitic origin. That the cardiac lesion persisted after a full course of antisyphilitic treatment might be due to the likelihood of the lesion being organic and irreversible, its extension having been temporarily prevented by the antispecific treatment the patient received. It is possible and even probable that contraction of "scar" tissue may eventually result in further limitation of function of the affected valve and/or that recrudescence of treponemal activity might result in further cardiac damage.

I W born in 1921 had no infantile or later symptoms of congenital lues until the age of 5½ years, when a rash appeared on the buttock which resulted in copper-coloured staining. This alone might not have suggested a syphilitic aetiology had we not known that a younger sister was being treated for congenital syphilis. A positive W R in the patient clinched the diagnosis, but the infection was probably acquired (see Chapter 13). Injections of stabilarsan were given and after the third injection the patient developed chorea which lasted on and off for 2 years. At the Rheumatism Clinic which she attended during this period her condition was diagnosed as "chorea with doubtful carditis." After three months her heart was moderately enlarged and a mitral systolic murmur had developed. By this time, at the age of $7^2/_{12}$ years, the patient had finished her antisyphilitic course of treatment, stabilarsan 9 G with protoiodide of mercury gr ¼ b d. during 21 months. The W R and Kahn reactions were then very nearly negative. At 9 years of age, when the W R. was quite negative, the child no longer showed any signs of chorea, but a soft apical systolic murmur was present and again at the age of 10. Finally when she was 11 years old Dr Sheldon's report was that the patient was free of rheumatism, with no chorea and nothing cardiac.

This is an interesting clinical history and one is almost tempted to suggest that the chorea and the cardiac condition might both have been of purely syphilitic origin. Whether this were the case or not, it is certainly legitimate to speculate whether or no the outcome would have been so favourable had the syphilis not been treated.

The following case is of considerable interest from several points of view

V B born in 1911 was seen by us in 1933 when his child aged 3 months, attended our V D Clinic with frank congenital syphilis (see Fig 21). There was *no history of venereal infection in Victor B* or his wife, but their blood serological reactions were strongly positive. The man appeared to be well when his blood was taken for the test. No history of any infantile symptoms of congenital syphilis was obtainable, but he gave a history of having suffered from "rheumatism and heart," so he said. He was transferred to an adult clinic where injections of neoarsphenamine (N.A.B.) were given. Ten days after the second injection (0·6 G) the patient is reported to have had an epileptiform fit, being unconscious for 10 minutes. When next he appeared at the clinic, exaggerated reflexes were the only physical sign present. The treatment was changed to bistovol (2 5 ml intramuscularly), of which he was given 3 courses each of 10 injections, with 4 to 6-week intervals between the courses. The blood was tested after each course *and still found to be positive*. Within a few weeks symptoms of meningitis developed, for which he was admitted to another hospital. Here the blood and C S F were found to give positive reactions. At

autopsy purulent meningitis (organism not determined) and lobar pneumonia were present. The mitral valve was incompetent and partly stenosed and had a ring of rheumatic vegetations. The aortic valve was also incompetent and distorted by fibrosis of long standing. Projecting from the wall of the left auricle were two partly calcifying caseous nodules surrounded by fibrous tissue and pronounced to be "probably syphilitic." The aorta exhibited a few plaques of atheroma around the orifices of the main branches. Sections of the brain showed, in addition to purulent meningitis perivascular cuffing and other changes suggestive of early general paralysis.

There can be little doubt, I think, that this man was a congenital syphilitic dying at the age of 23 of a purulent meningitis complicating an early stage of general paralysis. The heart lesions are of interest but difficult of interpretation. Unfortunately I did not see the autopsy but read the account of it afterwards. The nodules in the auricular wall were almost certainly gummata and if that were the case they were of treponemal origin. The cardiovascular lesions may have been of rheumatic origin, though there is nothing in the patient's history pointing definitely to rheumatism. On the other hand, the atheromatous plaques in the aorta around the orifices of the main branches in a patient only 23 years of age are strongly in favour of congenital syphilis, so that it is conceivable that the history of the so-called "rheumatism and heart" may really have been due to exacerbations of treponemal activity. In connection with the post mortem account that the mitral valve was incompetent and partly stenosed and had a rim of rheumatic vegetations, a publication on "Vegetations on Heart Valves" by Magarey (1949) is of interest. In many cases the tags of fibrin, originally described by Lambl in 1856 may become organized and attached to the auricular surface of the mitral cusps, leading ultimately to the gradual thickening of the cusps. They were not associated with any particular disease and Magarey suggested that they were part of the normal ageing process of the valve for they were not found in any of the 22 patients under 1 year and were *invariably* present in the 75 patients over 60. In mitral stenosis, he found deposits of fibrin in the angles between the cusps and suggested that progressive stenosis of the valve might follow upon organization of the fibrin. On the mitral valve in 250 routine autopsies Magarey found these fibrin tags in 85 per cent and it is quite possible that in the past some of these excrescences had been called rheumatic vegetations. In the case under consideration the cardiovascular syphilis present no doubt *gave rise to endocarditis and/or endarteritis, which might have* led to depositions of fibrin and the ultimate formation of what are commonly regarded as vegetations of rheumatic origin.

M.C. was born in 1916 after his mother's inadequate treatment in the second and third months of pregnancy. He was thus perhaps so far protected that he had no early infantile symptoms, but at 15 months developed anal condylomata. After irregular treatment with mercury, neo- and sulph-arsphenamine and bismuth over a period of 8 years, his blood and spinal fluid eventually gave negative Wassermann reactions at the age of 12 years. When he was 14 he began to complain of feeling faint and of pain over the heart. It appeared certain that a cardiac lesion was present, though its exact nature seemed obscure. There was a basal thrill and a systolic murmur which Sir Thomas Lewis, who investigated the patient with me, thought were probably due to a congenital heart lesion—a slight degree of pulmonary stenosis. Whatever the lesion may have been, it did not incapacitate the patient, for six years later he joined the Royal Air Force.

This is the only instance of congenital heart disease I have encountered in my series of cases of congenital lues.

Clinical significance of congenital syphilis of the heart

The literature of both pathological and clinical manifestations of congenital syphilis in the cardiovascular system has been given in some detail the few cases which I have encountered having a bearing on the problem have also been reviewed That there are so few cases is I think, attributable to the fact that my clinical material has been drawn from the under 12 age group with relatively few exceptions, whereas the more dramatic cases of this type in the literature are mostly adolescents and young adults In view of the wide diversity of opinions expressed by various authors in the past on this subject, an attempt must be made to summarize the present position and to make suggestions relative to the detection and management of these cases.

1 Myocarditis In infancy there is indisputable evidence of a diffuse interstitial myocarditis in many patients dying of congenital syphilis. Less commonly there may be a gummatous myocarditis and at times the gummata may show a myxomatous transformation It is possible that this *myocarditis may be one of the factors leading to neonatal death in these* patients, but there is no evidence on which to make any suggestions about its response to treatment. In young adults there are few definite cases on record of acute congenital syphilitic myocarditis leading to rapidly developing fatal cardiac failure. These have not been diagnosed during life and one cannot speculate on possible results of treatment. The possibility should however be borne in mind in cases of rapidly-developing heart failure in young people in whom there is no evidence or history of acute rheumatism or other more common aetiological factor (Warthin 1911 Friedlander 1921 and others) The possible significance of congenital syphilitic myocarditis is frequently overlooked and it is remarkable that the painstaking and extensive investigations of so able a pathologist as Warthin should not have received the recognition they merit. Perhaps it is because some investigators have been unable to confirm his findings, but Warthin particularly stressed the fact that much patience was needed in this type of research work and the necessary patience may not always have been bestowed upon it. In the author's clinic at the time when the clinical and pathological material was available it was unfortunately impossible to repeat Warthin's work owing to the lack of technical assistance Even though Rosahn has statistically demonstrated the error of Warthin's conclusions as to the alleged presence of syphilitic *lesions in presumably non syphilitic adults* by mistaking the ageing in the organs for syphilitic changes, there can I think, be little doubt of the validity of Warthin's observations on syphilitic infants, older children and young adults which have received confirmation from Stobie, McDonald, Turnbull and others. As I have indicated in this chapter and elsewhere in this book latent congenital syphilitics and *the children of congenitally-*

syphilitic mothers may be frequent bearers of types of syphilitic lesions and they may in the past have proved to be a significant source of error in the statistics of allegedly non-syphilitic individuals

1 Aortitis Small areas of scarring may be found in the aortas of children and adolescents dying from congenital syphilis and these have been shown microscopically to have been due to the treponema. The lesion found at autopsy in Case 3 (L.W p 128) was probably syphilitic, although proof cannot be considered absolute in the absence of demonstration of treponemata—an unlikely accomplishment after all the treatment the patient had received. Nevertheless as Warthin has emphasized, the collections of inflammatory cells, lymphocytes and plasma cells, in the form of masses or linear streaks between the tunica media and tunica adventitia or around the vasa vasorum, must be regarded as evidence of syphilitic involvement even in the absence of a spirochaetal form of the *T pallidum* Small lesions are unlikely to have any clinical significance, but if more extensive, they may lead to radiological evidence of aortic dilatation or very rarely to actual aneurysm formation with possible rupture. The age of a patient with aneurysm may sometimes be misleading and suggest that acquired rather than congenital syphilis is the cause. Carey Coombs refers to an authentic case of a woman who was undoubtedly a congenital syphilitic who died at the age of 48 of thoracic aneurysm The not infrequent association of atheroma and syphilitic aortitis adds to the difficulties of the pathologist post mortem as it had already done to the clinician during the patient's illness.

If the syphilitic process involves the aortic valve, aortic regurgitation will almost inevitably result and in any case of isolated aortic regurgitation in a young subject, in the absence of clear-cut history of rheumatism, the possibility of a syphilitic aetiology must be considered Thirdly the luetic process may involve the coronary ostia and give rise to the various manifestations of myocardial ischaemia, ranging from cardiac failure to rupture of the ventricle.

3. Congenital heart disease It has been pointed out that the evidence from the literature as to the causal connection between congenital syphilis and congenital heart disease is conflicting Nevertheless, the significance of foetal damage by maternal infections in the first 3 months of gestation has recently been recognized in rubella. Syphilitic infections early in pregnancy probably lead to abortion or stillbirth but if the mother is first treated at the end of the third month, the foetus may be damaged yet a live and non-syphilitic child result. Case 7 (M C p 131) is suggestive in this connection. The possible dangers of treating pregnant syphilitics in the fourth month is a subject calling for early investigation

4 Chronic valvular disease The occurrence of isolated aortic regurgitation as a definite if rare, manifestation of congenital syphilis must be accepted on the evidence presented in case reports. Congenital syphilis

of the mitral valve is perhaps less authenticated, the most definite reference to it being in Warthin's first paper (1911). He states that his 3 older cases showed mitral endocarditis with insufficiency and microscopic changes of syphilitic myocarditis, but he gives no further description of the macroscopic or microscopic appearances of the mitral valves. Cowan and Fleming and later Stoble refer to the possible causal relationship between mitral stenosis and congenital syphilis in some of their cases. The relationship between congenital syphilis and rheumatic carditis is important from two aspects. Clutton's joints are an undoubted manifestation of congenital lues but they are not invariably bilateral or painless, and I have seen several cases in which a unilateral painful knee joint in a congenital syphilitic child has been regarded as rheumatic and has led to prolonged rest in bed "to protect the heart." The second aspect to be considered is whether rheumatic fever occurring in a congenital syphilitic is likely to run an aggravated course or to be favourably influenced by anti-luetic treatment. Fordyce (1930) drew attention to the fact that children might be the victims of the double infection, congenital lues and rheumatic heart disease. Of 9 such cases which he described, a striking feature of 6 was the *latency* of the congenital syphilis. He put forward the suggestion that luetic rheumatic children form a well-defined sub-group of rheumatic children generally. "Any rheumatic child who shows unusual symptoms or perplexing physical signs or who does not respond satisfactorily to orthodox treatment for the rheumatism should have a blood test done and unless the result is clearly negative antisyphilitic treatment should be combined with salicylates. When rheumatism does affect an untreated syphilitic child the prognosis is almost certain to be affected and it is possible that 'many bad rheumatic hearts are based on congenital syphilis'" (Fordyce). Carey Coombs (*loc. cit.*) also expressed the view that congenital lues apparently predisposes to severity in an intercurrent rheumatic carditis.

Some of the patients whose histories I have given above would come into Fordyce's category, but I would go further and suggest that some of the attacks of so-called rheumatic carditis and even chorea may be manifestations of treponemal activity which would benefit by treatment on antisyphilitic lines even though the W.R. be negative.

This aspect of congenital syphilis has been rather fully dealt with because in my opinion it has not hitherto received adequate recognition. In my view a patient from the age of 7 years up to early adult life, say 30 years, who has signs or symptoms of circulatory disturbance or embarrassment, should be carefully investigated from the point of view of congenital syphilis. A negative serum W.R. must not be the final arbiter, as is still too often the case. The mother's blood should also be tested, the family history should be carefully inquired into, and I know from personal experi-

ence how much patience and tact this often requires and the inquiry should be carried out confidentially in the consulting room. Should the history be suggestive corroboration should be sought from an investigation of the patient's brothers and sisters uncles and aunts, and grandparents, if possible.

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THE ALIMENTARY SYSTEM

I. The Mouth and Pharynx

Mucous plaques were stated by Diday and other early writers on congenital syphilis to be not uncommon during the first few months of life These are seldom seen nowadays, doubtless on account of the ante-natal treatment of mothers and the earlier and more satisfactory treatment of infants. Other buccal lesions which have been described resemble aphthae, others the skin exanthem. Scrapings from aphthae would show the *Monilia albicans* whereas the secretions from mucous patches contain the treponema and are therefore infective. Occasionally in very young children deep ulceration of the dorsum of the tongue or of the fraenum linguae may be seen as was reported by Carpenter and others. Up to the age of 12 months condylomata may be seen on the cheeks, tongue or lips, granulomata on the tongue, and indurations of the lip all of which except the last are very uncommon. Jeans and Cooke record indurations of the lips in 79 out of 510 infants under the age of 2 years, many of them non-whites. In our experience indurations of the lip have been decidedly rare, but they may occur in association with mucous tubercles of the corner

of the mouth (see Fig 34). In this patient the condition started as an impetigo " after which a crust formed at the age of 6 months at the right angle of the mouth. Identical lesions may be seen in cases of acquired syphilis (see Fig. 95(a)).

The more tell-tale lesions in the mouth and pharynx arise a few years later as a rule, though occasionally the gummata of the palate or pharynx about to be described may not be seen until adult life is reached The lesions usually start as gummatous infiltrations (mucous patches) of the soft tissues, of the hard or soft palate, or of the faucial pillars or pharynx. They are not very painful they spread rapidly so that when seen for the first time the patient may exhibit quite an extensive area of ulceration with much necrosis and loss of tissue, frequently with a perforated palate and absence of uvula. In addition there may be a good deal of scarring about the oropharynx, with adhesions between the faucial pillars tonsils, the palate and the walls of the pharynx.



FIG 34 Mucous tubercle at right angle of mouth at 2⁷/12 years said to have been present since the age of 6 months The lesion looked granulomatous the lower lip was infiltrated and had yellowish exudate like lymph on the surface A similar lesion is shown in Fig 95(a) which came from a child with undoubtedly acquired syphilis. For teeth of this patient see Fig 48 on p 151

Fournier found the throat affected in 46 out of 212 cases (21·7 per cent) the most common site was the soft palate which he found to be exclusively affected in 30 of the 46 throat cases. The pharynx alone was attacked in 5 cases. The extremes of age were 5 to 25 years with the highest incidence between the ages of 10 and 17 years. Fournier states that, as with syphilitic disease of the nose, the condition starts insidiously in the throat and the damage to the parts may be considerable by the time the patient consults a doctor or the lesion is discovered accidentally as, for example, by a dental or throat surgeon. This silent onset of throat syphilis renders it impossible in many cases to give the precise duration of the syndrome.

On the other hand, Jeans and Cooke (p 164) observed lesions of the nose and throat in only 15 of the 329 children over 2 years with active syphilis studied by them (4 5 per cent). The ages ranged from 3 years upwards and the greatest incidence was between 9 and 13 years.

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with our experience of 40 years later He mentions erythema or infiltration of the mucous membrane of the mouth and pharynx with enlarged follicles in the pharyngeal wall. The mucous patches were seen on the uvula, tonsils and pillars of the fauces and they were rarely symmetrical they showed a great tendency to ulcerate and the larynx might be similarly affected as was narrated in the previous chapter Mackenzie stressed that congenital syphilis was an important cause of deep palato-pharyngeal ulceration in children—in fact this condition is nearly always the result of syphilis A peculiarity of these palatal ulcerations is their central position in the roof of the mouth and the symmetry of the area of destruction on either side of the mid line. In a small proportion of the cases ulceration of the tongue might be associated with pharyngeal and laryngeal ulceration.



FIG 35 Patient had necrosis of palate at an unknown age but the scarring of the soft palate with cleft in it and the displaced uvula were first seen when patient was about 10 years old (photograph at 28½ years) The teeth which were photographed at the same time showed only narrowing of the lower incisors, with small notches *in their cutting edges*

It would appear from Mackenzie's account that in his day the disease was more severe than during our own experience (1917–1939) for it attacked more young infants and the lesions were more extensive and destructive than in our patients He found for example, that out of 30 cases examined with reference to the period of invasion 14 (nearly one-half) occurred within the first year and of these 10 or one-third of the total occurred within the first 6 months In 69 cases, females were more frequently affected than males in the proportion of 41 females to 28 males. Of our 28 cases, 4 only concerned young children, 2 boys and 2 girls the other 24 comprised 11 males and 13 females, *the sexes being almost equally affected.* In 11 or nearly one-half the cases the age of onset from 3½ to 28 years, could be determined whereas in the remaining 13 the date of onset was unknown but the damaged palate or pharynx was discovered between the ages of 5½ and 12 years.

It is noteworthy how insidious the onset and how painless the course of syphilitic disease of the mouth and throat may be, so that when the patient first comes under observation, the cicatrization and damage to the palate (hard and soft) and pharynx may be quite extensive. Of our 24 *older* patients, 17 gave no history of infantile symptoms and of the remaining 7 only 2 had *definite* symptoms of congenital syphilis the first *had snuffles*

and epiphysitis, the second had snuffles and was small. The other 5 complained of such vague conditions as malnutrition, "always ailing," "having been a small or delicate baby" and one was born "with meningitis." The literature does not appear to disclose this absence of early manifestations of the disease with subsequent mouth and throat lesions.

It is also of interest to note that of our 24 patients no fewer than 14 had eye trouble, 13 interstitial keratitis and one cyclitis and iritis one of them had an attack of keratitis at 8 years and relapses at 12 and 32 years of age. Seven of the 24 patients complained of deafness and 5 of them had affected joints. About one-half of the patients had hoarse or gruff voices. Several patients with perforation of the palate spoke with a "nasal" voice like sufferers from a cleft palate. One patient whose voice had changed prior to attending our clinic was thought to have had diphtheritic paralysis.

Another patient, O.H., a girl aged 11½ years, had no serious illness until at the age of 10 years her throat became "ulcerated" and the ulceration spread rapidly She was sent to Great Ormond Street with the diagnosis of laryngeal tuberculosis, for which a hopeless prognosis had been given. The teeth and eyes were normal. There was scarring and fixation of the right side of the soft palate and a positive blood test confirmed the diagnosis of syphilitic ulceration. The activity of the disease was stayed by antisyphilitic treatment, her blood W.R. became negative in 12 months and remained negative until she was last seen at 20 years of age. She was then of fine physique and apparently well except for the scarred condition of her pharynx. The soft palate was completely adherent to the posterior pharyngeal wall, so that the secretions tended to collect in the nose at night. Although this interfered to some extent with her sleep surgical intervention was not advised by the rhinolaryngologists. The patient was unable to smell but could taste food.

This case exemplified the statement sometimes made that "syphilis of the mouth and throat may cause as much destruction in a week as tuberculosis may do in a year"

Among other interesting throat cases the following may be given

A girl was said to have had "meningitis from birth" but no details of any infantile symptoms were obtainable. At 12 years of age she developed keratitis when the serum reaction was found to be positive. While undergoing injection treatment for the eye trouble she developed ulceration of the throat and the treatment was stated to have been continued for some years, though of this one was unable to obtain any confirmation. The patient attended the Great Ormond Street clinic at the age of 23 years with her 9-months-old baby who had a simple conjunctivitis. The baby's blood test was negative then and for some years afterwards. The mother's throat was ulcerated and scarred, the palate perforated, and the uvula had disappeared.

D.R. was a small baby and suffered from snuffles. She had no other symptoms suggestive of congenital syphilis until an attack of interstitial keratitis occurred at 5 years of age following it was thought, the throwing of sand in the eyes. At the age of 10½ years she was admitted to the Children's Hospital under the care of Mr George Waugh on account of a "lump in the throat."

The relevant history was that at about 10 years of age patient developed discharging ears and became slightly deaf and the parents noticed that the child's breath was offensive A change in the voice was attributed to diphtheritic paralysis, but when the patient was examined by Mr Waugh the changed voice was found to be due to a scarred soft palate with a large cleft about which the parents had no knowledge (Fig 35) The otorrhoea had ceased and there was a chain of enlarged glands on both sides of the neck. In addition, about the level of the isthmus of the thyroid, to the left of the mid line, there was a firm rounded swelling attached superficially to the skin and to a slight extent to the trachea. It did not appear to be connected with the glandular enlargements or to be in the same series. The tonsils were enlarged and "dirty" adenoids were present. The growth in the front of the neck was thought to be either a gumma or a branchial cyst. The blood test was found to be strongly positive and after 2 courses of arsenical injections (4 G N.A.B in 12 doses) and the administration of syr ferri iodidi, the glands were much smaller and the growth in the neck had almost disappeared six months after treatment was started. The enlarged tonsils were removed six months afterwards they were very fibrotic and difficult to enucleate. Sections showed fibrosis in parts some muscle and salivary gland tissue was also present. The patient's hearing varied until one day when aged 15⁴/12 years, she suddenly regained her hearing in the left ear but not in the right. The improvement lasted for about 2 years and then the hearing deteriorated and again became variable. At 15 years of age the inflammation of the right eye recurred and it showed a slight nebula. The patient received 16·6 G of arsenicals in 46 injections and adjuvants in the form of thyroid parathyroid mercury and iodides over a period of 5 years (1920–1925), but the W R. was strongly positive for 12 years, after which it gradually faded to negative at the age of 27 years but the Kahn was still strongly positive. The patient had married in the meantime and the baby's blood gave a negative W R. and Kahn at the age of 7 months and again at 2²/12 years. On the last occasion the mother's blood had relapsed somewhat.

The next patient showed many features similar to the foregoing

D B a male, suffered no infantile symptoms, probably on account of the fact that the mother was receiving some treatment for the disease which had already been diagnosed in an older child. The first lesion D B. is known to have suffered was interstitial keratitis at 6 years, which lasted for more than a year and then apparently cleared. At 8 years of age he became deaf and when he was then examined at Great Ormond Street the palate was found to be ulcerated and scarred and showed a perforation. There was some improvement in the hearing after a few injections but owing to the war conditions and parental indecision treatment was allowed to lapse for 2½ years. When treatment was resumed hearing seemed to improve greatly at 12 years. At 15½ years of age the youth developed optic neuritis and choroiditis in the right eye, which rendered him practically blind in that eye. From this time on the deafness progressed in the left ear with occasional noises, while the right ear could still function. He was given spasmodic treatment at another hospital and by the time he had reached the age of 26 the serum reaction became negative but relapsed later At the age of 39 the W R. and Kahn test had become quite negative but the patient was very deaf in both ears. In spite of this handicap and a blind eye he was able to carry on his business and had two healthy children

An older brother also became very deaf and almost blind from choroiditis (see p. 231).

Lesions of the Tongue

Glossitis is not a common manifestation of congenital syphilis in children doubtless because the irritative effects of alcohol tobacco condiments etc., are not operative at that age.

Barlow in May 1880 exhibited a case of syphilitic disease of the tongue in a girl aged 6½ years who had deep ulceration of the mucous membrane of the tongue with a probable gumma in its substance. She had suffered from interstitial keratitis two years previously Still found the condition present in 4 per cent of his cases in some there was a patchy thickening of the epithelium In others ulceration—chiefly in the middle of the dorsal surface of the organ. The thickened area might have a washleathery look and be slightly raised above the adjacent area, or it might have the sodden dirty grey look of a condyloma, or the appearance might be dry indolent and yellowish-brown as if there were some gummatous infiltration of the superficial part of the tongue. In Still's experience such cases were usually seen during infancy—under the age of 2 years—but he records a case of chronic glossitis without ulceration in a boy of 3 years in whom the induration of the tongue was associated with anal condylomata.

Carpenter describes an ulcer of some depth far back on the dorsum of the tongue which was found post mortem but was not seen during life. In another infant 1 month old he found an ulcer of the fraenum linguae. In another patient 4 months old Carpenter found an ulcer at the posterior third of the dorsum of the tongue which was associated with infiltration of the ary-epiglottic folds and ulceration of the thyrohyoid membrane. Other authors have described lesions of the tongue—Fournier 4 cases of gumma in the muscular substance in patients aged 12 14, 16 and 24 years Hochsinger mentions having seen 3 examples of the diffuse sclerosing glossitis (v Duering) in one of which the whole of the tongue was affected and protruded from the mouth as with a cretin and in the other cases was in the form of localized nodules (gummata) which occupied one third to three-quarters of the organ.

Tanner in 1922 exhibited to the Clinical Section of the Royal Society of Medicine a child of 4 with syphilitic ulceration of the tip of the tongue and enlarged cervical glands. The lesion responded rapidly to treatment.

Among our cases a girl 7 years of age attended Great Ormond Street Hospital on account of ulceration at the corners of the mouth and mucous tubercles about the anus. The blood was found to react positively but owing to war time conditions (1917) she was treated only with mercury rubbings and soon defaulted Three years later she attended another hospital nearer to her home. She then had ulceration of the pharynx and tongue, for which she was given hydrarg c. cret. gr 1 t.d.d. Two months later the tongue was still ulcerated and stomatitis was present. The latter may have been due to the disease itself or to the mercury After a further interval of 2 months, during which time no treatment appears to

(*knospenform*) (Frey 1896 Pflüger 1924), *en trayons de vache* or teats of a cow (Sabouraud 1917) udder like (Oesipuntz 1927) and string purse (Mozer 1917) (*all quoted from Lebourg op cit* p 87).

Continental especially French observers interested themselves more particularly in the deciduous teeth which they maintained were frequently affected by congenital syphilis. It is probable that rickets which was formerly a frequent accompaniment of syphilis in infants, was the prime cause of the dental anomalies recorded. Parrot (1881) was the chief exponent of this view and he opined that the milk teeth were affected more frequently than Hutchinson surmised He maintained that many syphilitic babies died before they erupted any teeth and consequently the changes in the teeth which were often considerable, were hidden in the sockets Fournier (1886) agreed with Parrot that the deciduous teeth not infrequently showed typical Hutchinsonian characteristics but he added that the second dentition was much more frequently affected than the first, in the ratio of 15 to 1 Fournier also described and figured (pp 84, 85) types of 6-year-old molars to which Moon had previously drawn attention and which are hence known in the English speaking countries as Moon's molars, but in France as Fournier's molars." Cavallaro (1908–9) published the first comprehensive series of investigations on the teeth in congenital syphilis. *He confirmed Pasini's discovery* of the treponema in the dental tissues of a syphilitic foetus and stated that the parasite was abundantly present in the dental follicle near the vessels and in their walls. He included the multiple and symmetrical dystrophies of the deciduous teeth among the dental stigmata pathognomonic of congenital syphilis. He made many anatomical chemical and tinctorial investigations which have been extensively quoted but the present writer's dental colleague, the late A. T Pitts, wrote in 1928[1] I think much of what he says is far fetched and quite unwarranted Karnosh (1926) was of the opinion that Cavallaro was led to erroneous conclusions as regards the chronology of enamel hypoplasia. Kranz (1927) devoted many years to the study of the teeth for in his contribution to Jadassohn's monograph he states (p 255) that as long ago as 1898 and again in 1909 he reported that he had seen Hutchinsonian teeth in absolutely syphilis-free families *He further states that he was unable to find the treponema* in the dental follicles or teeth of 20 foetuses and children up to 5 years of age and that he was in consequence unable to agree with Cavallaro Pasini and others who attributed Hutchinsonian teeth and the other dental anomalies found in congenital syphilis to the local action of the treponema. In Kranz's opinion the chief factor in the production of dental as well as of bone and other anomalies was the disordered function of the endocrine glands occasioned by the treponema

Hochsinger (1924) considered congenital syphilis to be by far the

[1] Personal communication.

commonest cause of Hutchinsonian teeth, and he could recall only three instances in his own practice in which they were present in patients who showed no other sign of the disease. He thought they were due to an early attack of rickets. Morton Smith (1923) expressed the opinion that there were no characteristic changes in the milk teeth. He used the term mulberry molar apparently for the first time, for the type of Moon's molar whose crown consists of a number of diminutive tubercles or cusps, composed of imperfect or inadequately-calcified dentine and enamel. It has already been mentioned that Jonathan Hutchinson in 1858 referred to *the peculiar tubercular projections on the 6-year-old molars.* Smith does not share the view held by some that the changes in 6-year-old molars are more frequent and more diagnostic of congenital syphilis than are the Hutchinsonian incisors. Another American investigator, Karnosh (1926), reported the results of his studies on the histopathology of syphilitic dental hypoplasia. He disagreed with the French school that horizontal striations on the teeth might also be of syphilitic origin but he regarded them, as do most authorities in this country, as usually indicating periods of nutritional upset in early childhood. He found that indigestion, intoxication and nutritional imbalance associated with acute infections were the most common factors. Rickets was less often incriminated than was anticipated. Dentine and, to a less extent, enamel laid down in the first year, said Karnosh, was most affected, that laid down in succeeding years being progressively more healthy. Regarding the first permanent molar, an embryological study shows that while calcification of the enamel begins about a month before birth, such a deposit is limited to 3 or 4 isolated cusps or spicules, and it is never so advanced at birth that these cusps are well united by calcified layers. Among his conclusions he agreed with Hutchinson and others that Hutchinsonian incisors were due to faulty development and not to transient calcium deficiency.

Lebourg in 1939 published a monograph dealing with the teeth in congenital syphilis in which, in addition to recording his own observations, he gives a comprehensive survey of this interesting aspect of the disease. It is, however, distinctly flavoured with the views of Fournier, Milian and other French writers as regards the frequency of the disease and its relation to dental erosions and hypoplasia, and does scant justice to the observations of Moon, Pitts and other British observers. Lebourg himself, among other things, demonstrated the presence in a syphilitic foetus of treponemata between the adamantoblast cells, with consequent changes in enamel formation.

The English point of view was in part unfolded by Pitts when he opened the discussion on Oral Manifestations of Systemic Disease in Children at the Royal Society of Medicine, London, in 192[illegible]. The aetiology of the Hutchinsonian tooth was still obscure, he said. The fact that the stigmata were nearly always symmetrical, like the hypoplasia following

such a disease as rickets, suggested that there must be some central factor affecting calcification and producing the condition, as opposed to a local factor One did, however occasionally come across a case in which one central incisor was typically Hutchinsonian and the corresponding tooth on the other side was normal (Fig 45) Pitts was unable to offer any explanation of this curious fact (1921), but the present writer had for many years suspected that it might be due to the local endarteritis and/or periarteritis described by Cavallaro and others affecting one tooth germ and not the other



FIG 36 Showing *Treponema pallidum* in the developing tooth germ (× 1,000)
(Courtesy of Prof Robert Bradlaw)

The painstaking investigations of Bradlaw have lifted the causation and mode of production of syphilitic teeth from the realm of theory and speculation to a sound scientific plane. Bradlaw's convincing paper on the subject (1953) is illustrated by photographs of Hutchinsonian and Moon's teeth, Grenz radiographs ground sections of teeth, photographs of *T pallidum* in and around the blood vessels of dental follicles, and of hyperplasia, with anomalies, of the enamel epithelium Subsequent epithelial degeneration which occurs gives rise to the notch in the cutting edge, to the rounded angles of the incisor teeth and to the dome shape or small cusps of the Moon's molars. Other figures show endarteritis in the dental papilla of a developing tooth germ These dental changes are associated with and doubtless occasioned by the presence of *T pallidum* in the tooth germ (Fig 36).

With regard to the statement occasionally made that the deciduous incisors might show the typical Hutchinsonian characters, Pitts expressed his scepticism, since during the 20 years he had been connected with the Children's Hospital, Great Ormond Street, he had been on the careful

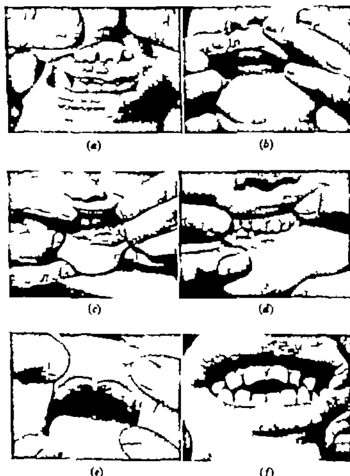


Fig 37 Six cases which showed types of notched deciduous incisor teeth. The first four patients were non-syphilitic patients, the last two were syphilitic aged respectively $1\frac{11}{12}$ and 5 years

look-out for such a case but had never seen one. This did not say that they do not occur but it at least warranted a doubt. He figured 4 upper deciduous incisors 3 of which were notched from caries. He had found that when the upper temporary incisors became carious, as they frequently did, the caries might start on the cutting side and produce a notch. On

superficial examination such teeth might be taken to be Hutchinsonian teeth, but they were never peg-shaped and were quite different from true Hutchinsonian incisors.

Six patients in my series of cases have shown notched deciduous incisors 4 of the children were definitely free from syphilis and in 1 of them (*b*) who was seen by Pitts, the notching was regarded as not being Hutchinsonian, but due to caries. The other 2 patients were definitely syphilitic (*e*) a girl aged $1^{11}/_{12}$ years whose deciduous central incisors were worn down to the gum in crescentic form, which might have been considered by the unwary to show the Hutchinsonian characteristics and (*f*) a girl 5 years old who suffered from haemoglobinuria and had positive Wassermann and Kahn reactions, and showed a mild degree of Hutchinsonian incisors (upper and lower) When last seen she had normal 6-year-old molars and one normal permanent incisor

The only feature of the deciduous teeth which should suggest congenital syphilis is marked hypoplasia. Early caries due to imperfectly formed enamel which may occur in this disease as in others, such as rickets, *measles, whooping-cough, etc. which affect young infants, is not very* helpful in diagnosis. Many Continental writers state that the eruption of the milk teeth may be delayed by congenital syphilis, but Carpenter Still and other British paediatricians think otherwise. The first teeth they say may be cut prematurely which is also borne out by the observations of Coleman who collaborated with Hutchinson in his early work. Coleman reported that in 11 cases where the information could be obtained, *2 had their teeth at birth, 1 at a few weeks, 2 at about 2 months 2 about* the usual time and 4 very late. An associated rickets might counteract the effect of a premature eruption of syphilitic teeth or even lead to a marked retardation. One of my syphilitic patients had erupted no teeth at 15 months, but X rays showed that the teeth were present in the jaws. X rays had disclosed signs of old rickets in the femur and tibia at the age of 7 months. Abnormal spacing of the *deciduous* upper central incisors is not uncommon, although *it is not so frequently present as it* may be in the case of the *permanent* upper and lower incisors.

Pitts maintained and my experience enables me to endorse his opinion, that the permanent teeth in congenital syphilis have considerable diagnostic value, yet there is a good deal of confusion about them Malformations which are not syphilitic are sometimes erroneously attributed to syphilis, and conversely the less characteristic Hutchinsonian incisors are frequently overlooked. The typical *Hutchinsonian incisor has two main* characteristics (1) an alteration in the architecture of the tooth so that its crown converges from the gum towards the cutting edge normally the borders of the tooth diverge from gum margin to cutting edge so that the actual volume of a syphilitic incisor is considerably diminished and (2) at the cutting edge there is a crescentic area of badly formed enamel or

the enamel may be absent, giving rise to a notch. These two features, Pitts stated were quite different from each other and were probably due to different causes The first, which affects the architecture of the tooth, must exist from the commencement of calcification down to the time when the crown is completely formed. The second feature exists to a variable extent and would appear to be a limited hypoplasia such as might occur in rickets or other general disease in which the nutritional balance was dis turbed Pitts graded syphilitic incisors into 4 groups which I suggest might be designated H^1 H^2 H^{2-3} and H^3 H^3 being the fully-developed and characteristic upper central incisors as originally depicted and de-



FIG 38 Teeth of a syphilitic girl aged 15½ years The upper incisors are slightly ab-normal (H^1) the lower incisors are hypo-plastic and spaced the tombstone' or "top-hat" teeth. These were from the patient with syphilitic lymphnodes men-tioned on p 269

scribed by Hutchinson in 1858 (see Figs. 43 44) In the H^1 tooth (Figs. 38 39) the edges are parallel like a pianoforte key or converge slightly the cutting edge is straight and the corners are rounded. Such teeth must not be considered *diagnostic* of congenital syphilis, as in fact they are not but they are sufficiently suggestive to justify a suspicion of the disease and the initiation of a thorough inquiry as set out on p 134. The H^2 tooth (Figs 40 41) is more narrowed than H^1 or it may be barrel or oat shaped with a slightly concave cutting edge, or it may be shaped like a screwdriver or chisel (H ^{3}) (Fig 42). The colour may be greyish and since the teeth are smaller than normal they will be spaced. The typical Hutchinsonian tooth H^3 has been so well described by Hutchinson

himself and by subsequent writers upon the subject that it is unnecessary to add to the original description (on p 142)



FIG 39 The teeth of a mother which led to the diagnosis of congenital syphilis in her case The upper central incisors are narrowed towards the cutting edge which shows a definite notch in the right and a straight edge in the left. There is a suggestion of a notch in the left lower canine These teeth I call H[1 2]



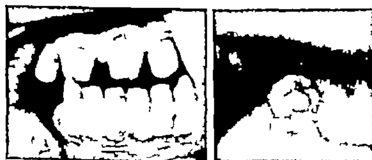
FIG 40 Upper incisors barrel shaped and with slight notching Lower incisors small and definitely notched one lower canine has a notch, the other a potential notch (H²) The school doctor had recently said the teeth were "*all right*" The *molars* were "Moon" with very small tubercles (mulberry molars) (Female aged 12¹/₁₂)



FIG 41 Upper central incisors barrel-shaped (H²) lower incisors normal from a female aged 12 years No infantile symptoms

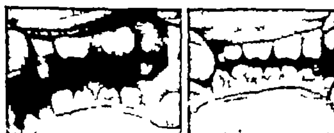
In order to clarify the confusion which apparently exists it is probably advisable to mention other points in connection with the teeth of congenital syphilitics which emerge from one's own observations. In addi

tion to Hutchinson's test teeth the upper lateral incisors may also show narrowing towards the cutting edge, with or without notching of that edge. Occasionally as in Figs. 49, 50 the central and/or the lateral upper incisors have a peculiarly solid look as of a truncated peg or cylinder



(a) (b)

FIG 42 (a) "Screwdriver" teeth showing also slight notching Lower incisors narrowed (H²) (b) The molars were typical Moon's teeth (1 shown) Male aged $11^{10}/_{12}$ years had bad snuffles as a baby haemoglobinuria at 3½ years, interstitial keratitis at 6 years



(a) (b)

FIG 43 (a) Typical Hutchinsonian teeth (age $6^{11}/_{12}$) Both upper central incisor teeth show "potential" notch. The lower central incisor teeth show narrowing of the biting edge and a good notch in each (H² ³)

(b) The "potential" notch in the upper central incisor teeth by the process of attrition has become an actual notch (H³) The lower incisors are as before Two of the molars were Moon's. The boy (aged $8^{10}/_{12}$) had latent syphilis The only infantile symptom was "failure to thrive

The absence of the upper lateral incisors has been regarded by Fournier and other observers as suggestive of congenital syphilis (Lebourg, p 47) but we have seldom encountered it. The canines, especially the upper pair may also be narrowed and notched, but in our experience this is not

so common as from Hutchinson's account it apparently was formerly The lower incisors are often markedly affected, sometimes even when the upper incisors show only H¹ characteristics. They are frequently

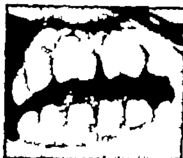


Fig 44. Typical Hutchinson incisors (upper and lower central) *in a girl of 11 years which were* overlooked by the doctor who recommended the patient to the clinic The *patient* had neurosyphilis, from which she died eventually at the age of 25½ years, although the blood and C.S.F had been negative for 12 and 14 years respectively Patient's mother died of general paralysis aged 38



Fig 45 One normal and one Hutchinsonian (H²) upper incisor The lower incisors are irregular and hypoplastic, with notches in two of them. (*Female aged 10 years*)



Fig 46 The lower incisors show exaggeration of the physiological notching and segmentation *sometimes mistaken for Hutchinsonian notching* The upper incisors were only slightly hypoplastic. Of the molars two were typical Moon teeth, one was normal and the fourth had been extracted Patient a congenital syphilitic, photographed at 8 years Father has G.P.I

small and spaced so that they resemble small tombstones or top-hats projecting from the gum with a straight or notched cutting edge which is sometimes narrowed (Fig 38) Occasionally the lower incisors are

thicker than normal with a convex anterior surface. Persistence of normal segmentation as seen in Fig 46 is sometimes diagnosed as syphilitic notching Figs. 37 to 54 are selected from photographs of our patients as being representative of the changes which may be found in congenital syphilis.



(a) (b)

Fig. 47 Teeth of a girl aged 9 7/12 years who was sent for treatment by the school doctor diagnosed as congenital syphilis The right upper central incisor is a typical H1 but the left tooth, although it narrows towards the biting edge, has peculiar notching All four molars were "Moon" (mulberry) with characteristic crateriform decay The girl was illegitimate and her own and the mother's blood gave a doubtful W.R.

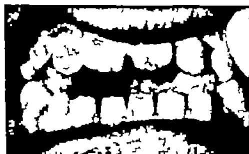


Fig 48 Teeth at 12 years Well-marked potential notch in the upper central incisors Hypoplasia (slight) and a potential notch in all the lower incisors The molars were "Moon" and showed crateriform decay Same patient as Fig 34

In 1927 Pitts wrote The dome-shaped first permanent molars described by Moon have a high diagnostic value but not so great as the maxillary centrals. The molars are affected by so many other conditions and the shape may be simulated closely by hypoplasia due to other diseases. The association of Hutchinsonian incisors with Moon's molars forms a



FIG. 49 Teeth of a child aged $8^4/_{12}$ years Unusual type of Hutchinsonian tooth (H²) Notched and somewhat hypoplastic upper central incisors thickened antero-posteriorly The child had a positive C.S F for over 5 years (with exacerbations) and both father and mother had tabes dorsalis The teeth were missed by the school doctor and by a dental hospital



FIG 50 Teeth of a boy aged 12 years The upper incisors all have a "solid" look, antero-posteriorly but enamel is poor in the distal portion of the teeth. The lower incisors are spaced and have small crowns with rounded edges (H²) The molars were "Moon's. Five years previously the upper incisors were described as being hypoplastic, the lower as being spaced notched and pegged (The patient had a macular lesion which was thought to be a glioma and nystagmus was a symptom.) (See p 339)

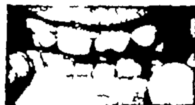


FIG. 51 Teeth of a boy aged 8 years The left upper central incisor shows a characteristic narrowed and notched tooth (H²) while the right shows only a potential notch (seen well with a magnifying glass) The lower central incisors are small and the right one is notched The lower molars were "Moony" and the left one had small tubercles (M²)



FIG 52 Upper central incisors H² with poor enamel in the distal portion Upper lateral incisors hypoplastic Lower incisors hypoplastic and the two central incisors show the notching of normal segmentation The molars had small cusps and were of the "mulberry" type Female aged 9 years

sign which is pathognomonic of congenital syphilis and, in my view is not produced by any other condition but the occurrence of Moon's molars alone with normal centrals, though highly suspicious, needs confirmation by other signs, and in their absence, if the W R. were negative, I should hesitate to conclude that they were caused by syphilis, though I should certainly suspect it. The tubercle of Carabelli, which is usually situated on the internal or palatal surface of the upper 6-year-old molar was formerly regarded as a sign of congenital syphilis, but this view has been practically discredited. Having been associated with Mr Pitts for nearly 10 years at the Children's Hospital and having had many dis-



FIG. 53 *Teeth of a boy aged 12 years* Not obviously syphilitic, yet the hypoplasia and spacing of the upper and lower teeth suggest syphilis Patient's treatment was much neglected at three hospitals until a fourth hospital sent him to Great Ormond Street. At the age of 8½ years his blood and C.S.F were both strongly positive. The C.S.F became negative at 11 years, the blood was almost negative during 15 months, after which the patient defaulted



FIG 54 *Upper central incisors* not obviously syphilitic, though the right has slightly converging margins enamel poor The lower incisors are suggestive of syphilis being spaced and hypoplastic (H^{0-1}) W.R. positive at $7^4/_{12}$ years when patient first seen as a latent familial case (Male aged 16 years)

cussions with him upon this subject, I am able to put on record my concurrence with many of his views. It has been stated previously that some particularly Continental, writers are of the opinion that Hutchinsonian incisors are not pathognomonic of congenital syphilis and that they may occur in the entire absence of the disease. Others maintain that a typical Hutchinsonian incisor (H^3) is specific to congenital syphilis, and Pitts statements that (1) a well marked Hutchinson incisor is as nearly specific to congenital syphilis as any physical sign can be, and (2) he had never seen the most typical form of this incisor in any case in which the diagnosis of the disease was not evident on other grounds, are borne out by my own experience On the other hand one has seen numerous adults with the less-marked incisor teeth, those I have designated H^1 and

H^2 in whom these tell tale teeth have induced me to probe for congenital syphilis—usually successfully In a minority of the cases, probably not more than 10 in all, the W R. was found negative—though this in an adult does not exclude the existence of congenital syphilis—and on physical examination and on anamnestic grounds no evidence of the disease could be *established* *One must emphasize, however* that in probing into family histories and taking blood tests from parents and sibs one has to be cautious as to one s questionings and investigations and on occasion one has had to desist although the trail appeared to be promising

How many congenital syphilitics have characteristic teeth?

Different authorities give widely divergent answers to this question, the reason being in my opinion the confusion which exists over what should be called a Hutchinsonian central incisor If the designation be restricted to the typical tooth Hutchinson originally described, then the proportion of patients showing such teeth will be small Of 208 patients above the age of 7 years attending our clinic, 32 (15 per cent) had typical H^3 incisors 83 (40 per cent) showed minor degrees of dental anomaly—H^1 and H^2 *the remaining 93 (45 per cent) had normal teeth. Most of the patients* with abnormal incisor teeth also had varying degrees of Moon s molars. Some of these minor dental anomalies are depicted in Figs. 52, 54, and it is obvious that they might easily be overlooked unless their occurrence as a possible manifestation of congenital syphilis had been stressed during the training of dental and medical students. The Fourniers found 43 per cent dental dystrophies in 480 cases. Jeans and Cooke in 463 cases above 6 years of age found dental hypoplasia in at least 40 per cent, and *they noted that most of the typical deformities, especially of the incisors* occurred in white children. Non-white children very rarely showed the characteristic Hutchinsonian incisors.

The effects of wear on the teeth

According to some writers notched incisor teeth are not erupted as such but are produced by attrition occasioned by use. This is true in some cases but by no means in all for the incisors may be notched on eruption and many observers including *Pitts and the writer have demonstrated by* X rays typically notched and narrow incisors in the maxilla before eruption Provided there is no malocclusion, which sometimes occurs in these cases, the defective enamel of the potential notch or of the mulberry molars disappears in time, leading to changes in the appearance of the affected teeth. The incisors show an *actual* instead of a *potential* notch (see Fig 43) and later still the edges of the notch may become worn down so that at the age of 25 or 30 years the central incisors may be shorter than they formerly were and show a straight cutting

edge By this time too these teeth appear to be less vulnerable to caries. The dome-shaped Moon's molars tend to retain their character but the papillae or diminutive cusps of the mulberry molars frequently show early effects of attrition and then present a flat or plane surface. On the other hand they may exhibit premature caries in the form of a black crater This crateriform decay of all the 6-year-old molars was regarded by Fournier (1907) as a suggestive sign of congenital syphilis other observers agree and we have seen it on several occasions in our syphilitic children.

The pathogenesis of syphilitic dental anomalies

Calcification of the milk teeth is almost complete before birth which explains why these teeth are so rarely affected At birth the first permanent molar is the only permanent tooth which has begun to calcify The permanent incisors and canines calcify during the first few months of extra uterine life, when congenital syphilis is usually most active, to which fact the involvement of these teeth and of the 6-year-old molars is to be attributed. As to the actual mechanism of causation of the dental deformities, it has previously been stated that Hutchinson originally attributed it to stomatitis, but in 1877 he invoked an arrest of development under the syphilitic influence. The demonstration of the treponema in foetal tooth-germs suggests the likelihood of a local action, either on the dental tissues themselves, such as oedema and elemental changes of the enamel and dentine (Bauer 1931 Lebourg 1939, Bradlaw 1953) or on the small local blood vessels primarily (Cavallaro Bauer Cruickshank and others) and secondarily on the dental tissues. Kranz and others hold that the dental dystrophies are the result of a general severe disease or metabolic disorder the commonest of which at birth and in early infancy is congenital syphilis. Rickets may also play a part. Other possible factors in the causation of these dental anomalies which have been suggested are dysfunction of one or more of the endocrine glands, the thymus, thyroid, sex glands and the pituitary (Kranz) the intervention of the nervous system (Lebourg p 108) and vitamin deficiencies (Trans. Xth French Congress of Stomatology 1938, Doin & Co Paris)

Although nearly 100 years have elapsed since Hutchinson first drew attention to the peculiar incisor teeth which are associated with his name and many subsequent authorities have written upon the subject, it is apparent from the foregoing account that there is still some diversity of opinion as to the causation and significance of the characteristic teeth associated with congenital syphilis. One's own view is that they are syphilitic in nature and are due to the direct effect of the treponema upon the developing tooth-germ together with its effect upon local blood vessels. Secondary effects due to general nutritional disturbances from any cause may also occur Typical Hutchinsonian teeth are in my opinion

pathognomonic of congenital syphilis and suggestive teeth (H[1] and H[2]) are frequently a sign of the disease which should not be disregarded

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III. Affections of the Salivary and other Racemose Glands

There had been various records of involvement of the parotid and other salivary glands in syphilis which were first summarized by Gerber (1913). He collected 37 cases, among which the parotid was involved 28 times, the submaxillary 7 times and the sublingual 6 times. Four of these patients were said to have had congenital syphilis. Haslund in 1916 brought the record up to date and Kemp and Moore (1922) in their summary of 65 recorded and personal cases of parotid involvement in syphilis, mention that 6 of them occurred in congenital syphilis. Occasionally the lacrimal gland may also be affected, so there may be a question of Mikulicz's syndrome, and in fact some writers (Thursfield 1914 Schaffer and

Jacobsen 1927) put syphilis among the possible aetiological factors concerned in producing this syndrome Garland and Thomson (1933) also give references to 3 cases in which the serum reaction was positive though this does not necessarily prove that the cases were syphilitic ("false positives"), and if they were syphilitic the syphilis may have been coincidental (Hird 1949)

Between the years 1921 and 1938 I came across 9 cases of parotid enlargement and had 3 patients in whom other glands were affected (Nabarro 1949) The patients varied in age from $2^{8}/_{12}$ years to 49 years. The condition presented some interesting features which earlier observers appear not to have noted. In several of the cases it was difficult to decide whether the swelling was really of the parotid tissue itself or due to enlarged lymphatic glands in, upon or deep to the parotid gland. When the attack was subsiding and for several months afterwards, shotty nodules could be felt in or upon the gland which were thought to be either lymph nodes or gummata of the parotid. Three of the patients had recurrences of the attack. The first of my patients to show the condition had his first attack (in 1921) when 9 years old and the second attack 8 years later His serum reaction had then long been negative after prolonged arsenical and heavy metal therapy and this second attack was diagnosed as mumps by his local doctor The lad's sister had a similar parotid swelling in 1922 when 7 years of age, and suffered no fewer than four recurrences in the succeeding 15 years This was the only instance in which parotid swellings were observed in siblings. Another patient, who had parotitis when 11 years old developed mastitis 15 months later while her blood reaction was still somewhat positive. The combination parotitis and mastitis had, according to Kemp and Moore, been recorded by one previous observer

Rather more frequently than the breast, the submaxillary and sublingual glands were affected, either alone or in association with the parotid gland. I have seen two such cases in congenital syphilitic patients, and an interesting one in a mother who probably had an oral chancre 2 or 3 months after marriage (before I saw her) in whom at each of 3 monthly intervals during her pregnancy about the time her period would have appeared, the sublingual gland was enlarged. Kemp and Moore do not relate if any of the 65 cases they refer to had recurrences of the swelling or exhibited the hard nodules in the parotid region after the general swelling had subsided.

Cappell (1936) drew attention to the fact, frequently overlooked that the finding of giant-celled follicles in a section is not necessarily diagnostic of tubercle. Giant cells may be found in other chronic inflammatory lesions, two groups of cases which may lead to confusion being (1) syphilis and (2) those associated with the absorption of fatty substances. One of the syphilitic cases he reports is of special interest. It concerns a young man, aged 21 who developed a swelling of the left parotid which

progressed rapidly for some weeks and led to facial palsy. A biopsy which was resorted to in order to diagnose possible malignancy revealed a granulomatous lesion with epithelial atrophy and numerous follicles composed of endothelioid cells and giant cells, many of the follicles showing central necrosis. The general picture was that of chronic interstitial inflammation closely resembling that observed in uveoparotid fever but without the eye lesions. While the patient was in hospital the right parotid became very swollen and a Wassermann test then taken was strongly positive. Confirmation of the syphilitic aetiology of the parotitis was forthcoming in the rapid regression of the swelling following anti-syphilitic treatment. Cappell makes no reference to a history of primary or secondary manifestations, so that one is justified in regarding the case as being probably one of congenital syphilis in view of the patient's age.

Two other papers are of interest in this connection. Adam (1939–40) stated that in nearly all his early and in many of his late cases of syphilis he had noted changes in Stensen's duct, oedema and congestion or swelling of the duct and adjacent area and an erythematous inflammation of the orifice. The pathology is to be explained, he says, by the swelling of the lymph-nodes which are present in the substance of the parotid and which presumably participate in the general adenopathy of syphilis. This may in time interfere with the flow of saliva from the gland and so lead to inflammation about the orifice of Stensen's duct, which Adam regards as a presumptive sign of syphilis.

Hamilton Bailey (1948), writing on the surgical anatomy of the parotid gland, refers to the fact that the parotid lymph nodes which are frequently stated to be within the parenchyma of the gland are actually extra-capsular, as is also the facial nerve.

There are doubtless other causes of recurrent parotitis, such as allergy (Bruce-Pearson 1935), pneumococcal infection (Payne 1940) and probably others, but from my own experience I incline to the view that the association of syphilis with parotitis is too frequent an occurrence to be a coincidence. If this type of parotitis should prove to be of viral origin, it would add another to the virus infections—herpes, poliomyelitis—which may be associated with congenital syphilis (see p. 294)

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IV Stomach and Intestines

Hoffmann (1908) described the occurrence of *T pallidum*, often in surprisingly large numbers, in the walls of the stomach and intestines of syphilitic foetuses and neonates. They are found in the muscularis mucosae and in the mucosa itself in association with the walls of the blood vessels and the gastric or intestinal glands. The parasites may give rise to little or no tissue reaction, or there may be areas of diffuse infiltration with syphilitic granulation tissue which may lead eventually to inflammation, fatty or necrotic exudate and even to ulceration. In infants who survive birth for longer than a few days, the invasion of the bowel wall is far less common than is that of the other abdominal viscera but it is probably of more frequent occurrence than is usually thought to be the case. The small ulcers may easily be overlooked, and even if observed they may not be suspected to be syphilitic unless specially stained for treponemata.

Henoch refers to two cases which occurred in his practice one an infant 7 days old in whom haemorrhages were found in the fundus of the stomach on the peritoneal and mucous surfaces the other a child of 9 weeks, in whom scattered effusions of blood were present in the mucous membrane of the stomach and bowel in association with cirrhosis of the liver and marked fibrosis of the gall bladder and bile ducts.

We have a record of only one case of intestinal ulceration with small ulcers in the small and large intestine, in an infant who died at the age of 6 months with acute syphilitic nephritis. At the time this case occurred (1920) facilities were not available for the systematic histological examination of all the tissues post mortem and for staining the treponema. In recent years, however (1946–48) when dealing with far fewer cases than were encountered during the years 1917–1937 Bodian has come across 2 cases of congenital syphilis in which ulceration of the bowel was present. The first was a baby three weeks old with a one-day history of diarrhoea. Post mortem the liver showed definite evidence of congenital syphilis. The oesophagus, stomach and duodenum appeared normal. The small and large intestines showed a number of transverse and longitudinal

ulcers, particularly in the lower ileum and upper colon. Treponemata were present in sections of the intestine (Figs 55 56)

The second case concerned an infant who developed a rash at 9 weeks, first on the face, then *spreading to the trunk and limbs*. *The blood* W R. was positive the cerebrospinal fluid normal in all respects. X rays showed the characteristic osseous lesions. The infant did well at *first on penicillin* treatment, then developed diarrhoea and died. At autopsy the stomach contained a little bloodstained material and there was no ulceration. In the ileum there were many slight erosions and a smaller number of deeper



FIG 55 Small intestine from a child aged 3 weeks (× 140) The mucosal surface is irregularly *eroded its basal portion is well vascularised and* is diffusely infiltrated with lymphocytes. The submucosa is thickened and contains more fibrous *tissue than normal and shows a similar infiltration*

(Courtesy of Dr. Marion Bodian)

ulcerations, all with congested margins. These bore no special relation to Peyer s patches Some of the deeper ulcers were bile-stained, as if they *were the result of necrosis. The peritoneal surface was not inflamed* The colon also showed a fair number of superficial erosions with congested margins No treponemata were found in sections of the liver kidneys or intestines, but such a result was to be expected in view of the fact that the patient had been treated. Practically the entire mucosa of the small intestine was replaced by chronic granulation tissue composed of new capillaries, numerous lymphocytes, eosinophils and fibroblasts. The submucosa was also *invaded in places by this granulation* tissue. The peritoneum showed oedema and perivascular aggregates of the same cells and

some vessels with perivascular cell sheaths also ran through the muscular coats. Auerbach's plexus and the ganglion cells were well preserved" (Bodian)

Vomiting diarrhoea, marasmus and malnutrition, which are frequent symptoms in syphilitic infants, are doubtless in some cases attributable to the lesions above described. Antisyphilitic treatment is as a rule followed by improvement in the child's condition from which it might be inferred that a syphilitic lesion of the bowel had been the cause of the trouble. On the other hand, antispecific therapy might so benefit a patient by its

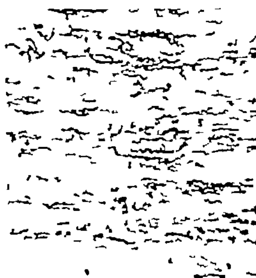


FIG 56 Treponemata in the muscular coats of the small intestine stained after Bertarelli and Volpino (1,000) from an infant aged 3 weeks. (Dr Bernard Schlesinger's patient)

general systemic effect that a non-specific enteritis could thereby be ameliorated or cured

Marasmus and malnutrition

Still (1931) mentions that von Hellwig, in 1722, recognized the possibility of infantile marasmus as the only symptom of an otherwise latent syphilis." Several authorities appear to have rediscovered this observation, but others, Findlay (1919) among them did not agree. I have records of more than a hundred syphilitic infants in whom marasmus was stated to have been present, and about 25 per cent of these patients died. In view of the results of Bodian's more detailed post mortem investigations recorded above it is practically certain that a more thorough examination

of the alimentary canal of our patients than was possible at that time would have revealed further cases of gastro-intestinal lesions In 28 of our cases marasmus appeared to be the only presenting symptom of an otherwise latent syphilis. In addition the presenting symptom in 4 other cases was pylorospasm (twice) and persistent vomiting (twice) These symptoms persisted, with remissions, for many weeks, in spite of various changes of diet, but they were checked when, after the patients were found to be syphilitic, appropriate antisyphilitic treatment was given. Similarly in the case of older children we have records of about a dozen patients, aged from 2 to 10 years whose only symptom of an otherwise latent syphilis was malnutrition debility or being considerably under weight. Improvement set in as soon as injections of arsenic or bismuth were given.

Rectal lesions

Mucous tubercles and condylomata may occur at the lower end of the digestive tract as at the upper but in our experience they have been rare. A premature infant who died at the age of 3 months after a haemorrhagic type of the disease was found to have a hypertrophied and ulcerated rectal mucosa. Treponemata were found in the perianal skin, as well as in many of the internal organs (see p 93). These rectal and anal lesions may give rise to great pain on the passage of faeces so that the infants scream when endeavouring to pass a motion or they may become very constipated through a reflex inhibition of bowel activity The ulcerations around the anus may radiate as they do round the mouth, and the scars or rhagades are permanent stigmata of this disease.

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V The Solid Abdominal Viscera

(a) *The Liver*

The earliest phases of the hepatitis of congenital syphilis are to be seen in syphilitic foetuses and neonates. The liver being the first and biggest of the foetal organs to receive the impact of the treponemal invasion from the placenta, it is not surprising that it usually shows more marked pathological changes than does any other organ in the syphilitic foetus.

The reaction to the treponema is the same in all the tissues and organs and closely follows the pattern of the reaction of the adult tissues in acquired syphilis In the liver it manifests itself as a diffuse interstitial round-cell infiltration which is obviously associated with the smallest blood vessels and with a massing of the treponemata in the perivascular connective tissue. This cellular infiltration is often succeeded by a varying degree of fibrosis or cirrhosis, which ultimately leads to con traction of the organ or tissue. The reaction may sometimes be so severe in syphilitic foetuses as to render organs, particularly the liver and lungs, unidentifiable under the microscope. Another reaction to the treponema is a retarded development of various organs which goes hand in hand with the overgrowth of the interstitial connective tissue. Most authori ties hold the view that the interstitial inflammatory reaction is primary and the retarded parenchymatous development secondary Others, however hold that the retardation in the parenchymatous development is primarily produced by the treponema itself and/or a presumed syphilotoxin, and that the overgrowth of the interstitial connective tissue is a secondary manifestation

Gubler (1849) was the first to record the changes in the liver of syphilitic infants. He described it as le foie silex avec les grains de semoule — the flint like liver with semolina grains—but this description really applies to the late stage of a generalized cirrhosis such as may be found in children who have survived birth for some weeks or months. Clinically the liver is somewhat enlarged has a smooth surface, is moderately firm in con sistence and does not, as a rule appear to be tender Jaundice may some times occur and more rarely ascites. In the less severe forms of the malady and if treatment is given early the condition is curable and the patient may recover

Hutinel gives a detailed account of the different stages in the develop- ment of the liver changes in congenital syphilis. Enlargement of the spleen is usually but not invariably an accompaniment of an enlarged liver and enlargement of both liver and spleen in an infant was formerly regarded as being very suggestive of congenital syphilis. Sometimes there is no macroscopic evidence of any disease in the abdominal organs of these foetuses and neonates, but they are usually enlarged and may be of firm consistence It must be remembered, however as Still pointed out and as has been confirmed by our own experience, hepatic syphilis, whether in the form of diffuse cirrhosis or of small syphilomata, is often undiagnosable clinically and even at autopsy a diffuse cirrhosis may be overlooked unless the organ is examined histologically

Post mortem the surface of the liver is usually smooth, but may be finely granular its colour red or yellowish brown, with minute pale areas up to the size of a pin's head frequently scattered throughout its substance. These tiny nodules represent areas in which the liver cells surrounded by

inflammatory cells, are undergoing degenerative changes from cloudy swelling to actual necrosis. They were called by Virchow miliary gummata and they are analogous to the earliest phase of the miliary tubercle. They are now usually known as miliary syphilomata. Larger lesions, which have the structure of gummata and are analogous to a caseating tuberculous lesion, are rarely met with in syphilitic foetuses and neonates. Carpenter records only one case of gumma of the liver in a child of 8 months, and Hutinel states that he has seen only one case of well marked gumma of the liver in a newly born infant.

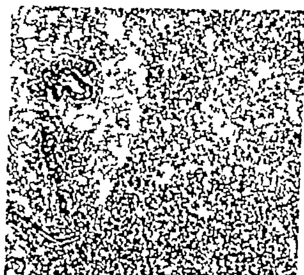


FIG. 57 Portion of a liver lobule from a child aged 9 weeks showing thickening of the portal tract by fibrous tissue which also spreads into the lobule producing a pericellular fibrosis (45) The collagenous tissue is infiltrated with plasma cells and lymphocytes The parenchymal cells are irregular in shape and a few are multinucleate (Dr R T Brain's patient)

Sections of these livers appropriately stained may show newly formed fibrous tissue within the liver lobules and even between the liver cells—the condition being known variously as uni or pericellular or intralobular cirrhosis (see Figs. 57 58) The liver sinusoids are frequently dilated and may contain normoblasts, megaloblasts and other evidences of blood formation The persistence of haemopoiesis, even up to the age of 3 months which may be seen also in the kidneys, suprarenals and, more rarely in other organs, is evidence of the retarded development previously alluded to. Many treponemata can be demonstrated in the interstitial tissue and between the liver cells[1] some of them are normal in appearance

others exhibit various degeneration forms such as club shapes and granules. It is often difficult or impossible to demonstrate treponemata in the tissues of infants who have received antisyphilitic treatment during life. Occasionally at autopsy ascites, perihepatitis and perisplenitis, with or without flakes of lymph may be found.

The relevant microscopical findings at autopsy in 50 syphilitic children under 1 year old are shown in Table 7. In only 3 or 4 of these cases was there a history of jaundice and it was never severe or persistent.

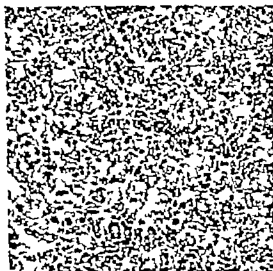


FIG 58. Section of liver from a child aged 3 weeks showing pericellular fibrosis. The intercellular trabeculae are composed of fibrogranulation tissue containing plasma cells and lymphocytes (× 70)

Other causes of hepatic cirrhosis in infancy

Certain of the older writers (Henoch, Carpenter) described cases in which the physiological neonatal jaundice failed to disappear but became more marked and persisted until the patient's death after an interval of from 2 to 5 months. There were manifest signs of congenital syphilis during life and at autopsy the liver was cirrhotic, and in at least 2 of the cases the gall bladder and bile ducts had been transformed into fibrous structures which filled the portal fissure. Clinically the signs were those of congenital absence or atresia of the bile ducts which itself may lead to a biliary form of cirrhosis.

It is pointed out on p. 242 that the erythropoiesis which may be observed in neonatal conditions, and which is greatly increased in erythroblastosis foetalis, is differentiated from that due to congenital syphilis in that in

the latter disease much of the portal and renal haemopoiesis is of a lymphocytic and plasma cell type (Gilmour) The constant blood destruction which takes place in erythroblastosis foetalis leads to a varying degree of liver damage, ranging from deposition of pigment (haemoglobin bilirubin) to cirrhosis and possibly even necrosis. Cirrhosis of the liver is a rare complication of erythroblastosis foetalis (Lightwood and Bodian) Fig 59 is an illustration from one such case.

Even if the two diseases, congenital syphilis and erythroblastosis foetalis, should coexist, which Gilmour and Hawksley and Lightwood have shown may sometimes be the case it does not follow that fibrosis of the

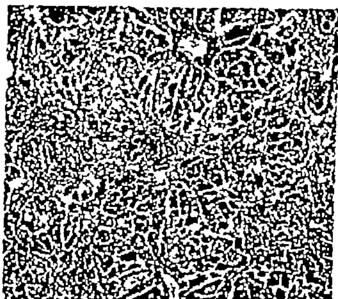


Fig 59. Cirrhosis of the liver in a case of erythroblastosis foetalis (Lightwood and Bodian) (60)

liver must necessarily be an accompaniment, for in Hawksley and Lightwood's case there was no fibrosis and in our case of jaundice which survived (see p 243) and was diagnosed as one of icterus gravis neonatorum, there was no evidence of liver damage

Diffuse perilobular and sometimes even intralobular cirrhosis without evidence of congenital syphilis, may be seen at birth, in infancy or in older children, often after prolonged jaundice associated with viral hepatitis (Bodian and Newns).

In syphilitic patients who survive, the liver fairly quickly diminishes in size and as was pointed out by Barlow many years ago, usually reaches normal size before the spleen In the majority of these cases the liver and spleen are no longer palpable by the end of the first year of life If

by that time the organs are still enlarged the patient may become anaemic and present the clinical picture of the von Jaksch syndrome. Four such cases which we saw in our clinic will be considered later (see p 239). On the other hand, we had 2 patients, aged respectively $2^{8}/_{12}$ years and $3\frac{1}{2}$ years, in whom the liver was definitely enlarged yet receded so as to be no longer palpable 2 years later

TABLE 7

Microscopical Findings and Associated Lesions in 50 Syphilitic Infants under 12 months examined at Autopsy at the Hospital for Sick Children

(*A*) 41 cases under 6 months.

Microscopy reports available in 34 cases

Intercellular fibrosis, either alone or with other lesions	19
Dilatation of liver sinuses and haemopoiesis	9
Fibrosis around portal canals—with other changes	6
Fatty change of liver cells	5
Thickening of hepatic arteries	2
No obvious signs of disease	3

Note Some patients showed more than one pathological change.

(*B*) 9 cases aged 6 to 12 months.

Microscopy reports available in 7 cases

Fatty change in the liver cells	2
Cirrhotic changes	1
Early portal fibrosis	1
No syphilitic lesions	3

In the 50 autopsies the following associated lesions were encountered

Perisplenitis	7 cases
Perihepatitis	"
Ascites	4
Pericarditis with effusion	case
Nephritis (clinical or pathological evidence)	6 cases (under 8 months)

Finally we come to older syphilitic children from 7 to 10 or more years, in whom the liver was so enlarged and firm that a definite diagnosis of cirrhosis of the liver was made. Jaundice and/or ascites may be a symptom in such cases. Gummata have also been recorded but we have not observed them in children of this age. In all, we have seen fewer than half a dozen cases in which cirrhosis of the liver has been diagnosed and as they all exhibit features of interest in addition to the liver condition, a somewhat detailed description of them may not be out of place.

A.B was healthy until 5 weeks old, then had rash, snuffles and marasmus. He was treated with mercury as an outpatient for a year but did not do well. At $2\frac{1}{2}$ years he is said to have suffered from rickets. His tonsils and adenoids were removed at 5 years of age. When nearly 8 years old he began to complain of "pain in the right side" for which he attended a nearby hospital for nearly a year As he was showing no signs of improvement his mother brought him again to Gt. Ormond Street Hospital which he had attended for a year in early

infancy On admission there was an obvious swelling in the epigastrium which was caused by an enlarged, firm and coarsely irregular liver which in the right nipple line extended to 3 fingers breadth below the costal margin. The spleen was also palpable 1 finger s breadth, firm and painless. The kidneys could not be felt. The cardiac and respiratory systems seemed normal. There were several carious teeth but none showed Hutchinsonian characteristics. The optic fundi were normal and there was no choroido-retinitis. There was no apparent abnormality of the central nervous system The cerebrospinal fluid was normal at 8½ and again 3 years later Telangiectases were noted on the cheek and right hand and forearm. Urea concentration was good and the laevulose test of liver function gave results within normal limits. The clinical diagnosis was *cirrhosis of the liver* and as the W.R. was strongly positive the *hepatic condition was regarded as being syphilitic* It was considered to be risky to give injections of arsenicals, so the treatment in the ward was with protoiodide of mercury first ¼ gr t.i.d then gr ½ for a week and then gr ¾ for several weeks. The boy was then discharged from the ward and attended the outpatients department for 3 months, during which time he was treated with liq hydr perchlor and pot. iodidi. As the blood W R. was still very strongly positive and the liver showed no sign of diminishing in size or consistence, it was decided to see what the cautious administration of arsenic could effect. Five courses, each of 8 weekly intramuscular injections of sulphostab were given, with intervals of 1 month between the courses. In all, the patient received 6·25 G of the drug and protoiodide of mercury spread over 13 months, when the physician in charge thought the liver condition had improved The mother said the boy was distinctly better and that he had no more pains over his liver or in his abdomen generally The W R. remained strongly positive. He was then given bistovol (24 ml. in 19 injections) and by this time the titre of the W R. appeared to be on the wane. The boy was again examined by his physician, who considered that there was much improvement, as "the liver was just palpable and not nearly so irregular or hard as it had been As the W R. increased in titre at two 3-monthly tests it was decided to try the effect of heat therapy He was given malaria, but during the second bout of fever he became delirious, so the malaria was stopped and T.A.B vaccine injections substituted. Next he was given 37 5 ml bisoxyl (bismuth oxychloride) in 32 injections, after which the Wassermann reaction showed definite signs of improvement, until eventually it became negative for the first time at the age of 20. But we are anticipating somewhat. Just before he was 12 years old he fell from a wall and knocked his head, which resulted in an attack of polyuria and polydipsia, for which he was again warded. While in the ward the polyuria dropped from 100 oz. to 50 oz (2 8 to 1 4 litres) in 24 hours. When seen a few months later he was very well the polyuria had disappeared, he was a swimmer and his mother said he was "vastly better Nevertheless the liver was again 2–3 fingers breadth below the costal margin. He was last seen at the age of 21 just before the second world war when he was of fine physique and said he was going into the army His W R. was then negative We have not seen him since 1939.

B F was born in 1922 and is said to have been a healthy baby until about 3 years of age when the mother noticed that the glands in the neck were swollen. For this she was given sunlight treatment for 3 years and during the course of this treatment (between 3 and 4 years of age) she began to attend an eye hospital which an older sister was then attending on account of interstitial keratitis. As the enlarged cervical glands failed to respond to 3 years sunlight treatment the patient was taken to the tuberculosis officer under whose care she was for

the next 4 years. The tuberculosis officer was unable to find any evidence of tuberculosis, and the patient was eventually brought to Great Ormond Street at the age of 10½ years. During the years that the patient had been under observation, nobody apparently had thought of correlating her enlarged cervical glands, her eye trouble at 3–4 years of age (which was probably interstitial keratitis), and her sister's eye trouble, which was undoubted interstitial keratitis. Even the paediatricians were nonplussed for a time. The outpatient physician's comment was "Anaemia ? cause. Cervical adenitis. Liver much enlarged, spleen not felt. Teeth good." The girl was almost immediately admitted to the wards for a thorough investigation. Nothing abnormal was found in the heart or lungs. The teeth were not mentioned, though it will be seen from Fig. 38 on page 149 that the lower incisors in particular are very "suggestive" of congenital syphilis. The liver was considerably enlarged—3 to 4 fingers breadth below the costal margin—and slightly tender. The spleen was just palpable. Many lymph-nodes in the cervical region were enlarged. A blood count showed a hypochromic anaemia and the diagnosis was thought to rest between lymphadenoma and acholuric jaundice. A fragility test of the red corpuscles was within normal limits. Shortly afterwards a gland could be felt in the right axilla and in the right iliac fossa. A cervical gland removed for biopsy showed foreign-body giant cells (see Fig. 82), which at first sight seemed to be tuberculous in nature but no tubercle bacilli could be detected. The section is described more in detail on p. 267. Mantoux tests at 1 in 1,000, 1 in 100 and 1 in 10 were all negative.

When at last we saw the patient the teeth were sufficiently suggestive to justify taking blood for a Wassermann test. This, as was to be expected, was strongly positive and the patient was started on cautious treatment with liq. hyd. perchlor. ℳ xx (1 in 1,000 1.3 ml.) and pot. iod. gr. v (0.3 G.) t.i.d., with the result that her general condition improved and she gained 8 lb. (3.6 kg.) in weight in 5 weeks, when she was discharged from the ward to attend the special V.D. clinic. She now received 5 courses of sulphostab injections (14 G. in 39 injections) with the mercury iodide pills, 32 injections of bismoxyl = 57 ml. and 16 injections N.A.B. = 6·8 G.—all over a period of 3 years. The W.R. became weaker and by 1940 (at 18 years of age) was negative but relapsed again in 1941 and in 1943 when the patient was last seen. At about 12 years of age the patient had a relapse of her interstitial keratitis. The liver and spleen were still enlarged (the former down to 1 in. (2.5 cm.) below the umbilicus), as were also many of the lymph nodes. A repeat Mantoux test was again negative at 1 in 10 dilution. When last seen at 21 years of age the liver was not felt and the cervical glands were still slightly enlarged.

I.P. was born in Feb. 1912. She had no infantile or early symptoms until she became very thin at 18 months of age; at 2 years she developed sores round the mouth and on the chin which bled considerably and consequently left scars (rhagades). "From infancy" the eyes were constantly watering, from which the mother concluded that the "tear duct was blocked." At 2⁸/₁₂ years her eyes started to be inflamed and she attended an eye hospital for 2 to 3 years. No injections were given, the patient receiving only local treatment for the eyes. Next she was treated for 3 years by a private doctor with grey powders, but as she complained of considerable pain after taking food she was referred to Great Ormond Street at the age of 8½ years. Here she came under the care of Dr. Langmead, who found the liver very considerably enlarged and firm, and the spleen somewhat enlarged. Her subsequent history until the patient defaulted in 1929 has already been related on p. 112.

The following case exemplifies the difficulties which may confront the practitioner in this type of hepatic case.

K.L. was born in 1925 as a result of the mother's seventh pregnancy 5 of which terminated in miscarriages. The mother had been examined and treated for syphilis after the first 2 miscarriages and since her treatment she had had one miscarriage, a healthy child and 2 more miscarriages before the patient. The patient K.L. was well until he was a year old then he had pneumonia and "meningitis" followed by epilepsy He attended the outpatients clinic at the age of 1½ years for ? petit mal and he improved on luminal. No blood test was taken at the time from either mother or patient, which is a regrettable omission, for it not infrequently happens that a syphilitic mother with a positive blood test, may have an epileptic child who when it is serologically examined more often than not gives a negative blood test. There was a history of deafness at the age of 7 following an injury to the head. The eyes showed no choroido-retinitis, and as there is no note on the teeth in the records of the case, these were almost certainly not markedly abnormal. When seen at our clinic, the mother's W.R. and Kahn reaction were positive but the child's were negative on two occasions at 8 and 9 years of age and gave a weak positive (? a non-specific reaction) between those dates. The cerebrospinal fluid at 8 years of age was normal in all respects. He was treated with stovarsol orally for 6 months during the year and with a limited amount of phenobarbitone. During the whole of that time he had no further attacks of epilepsy and his hearing improved When nearly 9 years of age he was examined after an attack of "influenza, when his liver was found to be 2 fingers breadth below the costal margin and to have a hard edge. Unfortunately that was his last attendance but one at the clinic, so that his further history is not available. The father was 17 years older than the mother was an old soldier had had a "stroke, high blood pressure and valvular disease of the heart"—so he was almost certainly the cause of his wife's syphilis manifested shortly after marriage. The patient K.L. would probably have shown a positive blood test had this been examined in infancy or early childhood and there can be little doubt that his epilepsy and deafness both had a syphilitic basis in his mother or himself or both. The hard, enlarged liver may also have had a syphilitic basis and it is unfortunate that its subsequent condition could not be followed up

As long ago as 1926 Hutinel wrote (p 245) that the liver like many of the other organs and tissues of the body may often become sensitized by the congenital infection so that non specific infections or intoxications have a profoundly disturbing effect upon it, which may be clinically obvious and requires antispecific treatment. Subsequent writers have agreed that various other manifestations of congenital syphilis, for example interstitial keratitis, Clutton's joints, late cerebrospinal lesions, may likewise be evidence of an allergic hypersensitive condition

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(b) The Spleen

Enlargement of the spleen was formerly regarded as a cardinal sign of infantile congenital syphilis. Gee (1867) found that one half his cases were thus affected. Barlow (1877) thought this was an underestimate, for he found splenomegaly in 78 per cent of his cases. Coutts (1896) reported definite enlargement in 62 per cent and thought that the size was probably above normal in a further 19 per cent making a total of 81 per cent. The splenic enlargement is not always present at birth for Mewis (1879) found it in 78 per cent of macerated foetuses and in 76 per cent of neonates

Still (1908) found the spleen easily palpable in 45 per cent of his cases of congenital syphilis, and 1 in below the costal margin in 22 per cent, from which he concluded that the absence of splenomegaly could not weigh much against a diagnosis of syphilis, but in association with other suggestive symptoms its presence was of some confirmatory value In our experience the enlargement of the spleen was found in fewer cases than Still recorded from which it appears to follow that with the reduction in the severity of the disease during the last few decades the spleen is less likely to be enlarged than was formerly the case. As indicated in the previous section, the splenomegaly is usually though not always, accompanied by hepatomegaly After the age of 6 months the advent of rickets may complicate the picture and be an added cause of splenic enlargement.

Pathologically the capsule may be found thickened, with fibrous extensions into the substance of the organ. The blood vessels may show specific peri and endarteritis, with considerable thickening of their walls and as a result fibrotic changes may occur in the Malpighian corpuscles Perisplenitis is not uncommon but gummata are exceptional. As a rule, with the improvement in the condition of the patient, the spleen diminishes in size so that it is no longer palpable at the age of 1 year Sometimes, however the spleen instead of shrinking becomes greatly enlarged, associated with enlargement of the liver and a considerable degree of anaemia Four such cases between the ages of 1 and 3 years which came under our observation are described later (p 239). Personal cases of enlarged spleen associated with enlargement of the liver in older children have been referred to on p 169. They serve to show that in cases of chronic enlargement of the liver and spleen in older children and adolescents, syphilis as an aetiological factor must be borne in mind.

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(c) *The Kidneys*

(1) Pathological changes in the kidneys of syphilitic foetuses and neonates

In the syphilitic foetus and neonate the kidneys, like most of the other organs may contain many treponemata which give rise to reactions similar to those seen in the other viscera. In the peripheral part of the cortex and in the medulla evidences of arrested development may be seen, such as immature glomeruli areas of abnormal tubule formation small cysts of the cortex and foci of haemopoietic tissue The other reaction to the treponema is of the usual syphilitic type, starting as a periarteriolitis and spreading from the tunica adventitia to the adjacent connective tissue. This is soon followed by a cellular infiltration which consists mainly of small round cells with some polymorphonuclears and histiocytes, arranged as tracks or cuffs along the vessels. Hutinel, who made a special study of the renal lesions in congenital syphilis, states that the glomeruli and tubular epithelium remain unaffected for a time and the lesions may not pass beyond the initial stage either because the patient dies from the severity of the infection or because the lesions disappear after birth when under the influence of the milk diet, the renal excretion becomes more active.

(2) Syphilitic nephritis in infancy

Various authors have reported cases of syphilitic nephritis in infancy — Hochsinger 1898 (and others cited by him, *loc cit.*, 1927), Carpenter 1901 Still 1908 Lange 1919, Hutinel 1919, 1922 Frank 1922, and others. A clear clinical picture has been drawn of this condition, but the pathological aspect has been confused by attempts to fit the syphilitic nephritis of infants into preconceived classifications of renal disease. It must be borne in mind that symptoms and signs which were formerly held to be diagnostic or suggestive of renal disease are no longer to be so regarded For example albuminuria and the passage of casts and of occasional red blood corpuscles may occur in infants with severe gastro-enteritis, and oedema may be present in markedly dehydrated patients. In a profoundly ill child be it syphilitic or suffering from some other infection the blood urea may be raised to as much as 60 mg per 100 ml (as it was in one of the cases given in Table 8) without this being conclusive evidence of nephritis

At the Hospital for Sick Children between 1917 and 1939 we saw 12 cases of infantile syphilitic nephritis Two of these cases survived one in whom the condition was diagnosed at 2½ months and who was given a bad prognosis, the other who at the age of 4 months was apparently moribund on admission to hospital These two recoveries having been

unexpected an account of them is deemed worthy of being put on record, for in the pre penicillin era recovery from infantile syphilitic nephritis was a very rare event.

A.M was born in August 1921 The father was treated for syphilis in 1918 and after 7 intravenous injections of arsphenamine and 7 intramuscular injections of mercury the W.R. became negative and was still negative in 1921 The mother had no symptoms or signs of syphilis the child was born 6 years after marriage and there were no previous or subsequent pregnancies down to 1928 when the family defaulted. The patient snuffled at 2 weeks at 7 weeks he suffered from diarrhoea and vomiting, and when about 10 weeks old, the day before he was brought to hospital, there was swelling of the hands and legs, of the lower part of the abdomen and scrotum. The child was passing very little urine and Dr Still under whose care he was, gave a very bad prognosis For several weeks he remained in this precarious condition and as his W R. was strongly positive and the nephritis appeared to be due to syphilis, small weekly injections of sulfarsenol (2 centigrammes each) were given for 10 weeks, with a month s interval after the first course of 6 injections. On one occasion after an injection of 35 mg there was a rise of temperature to 100 F and 102 F Both ears became infected from nasopharyngitis, and at the age of 5 months a peritonsillar streptococcal abscess was opened a week later the child developed erysipelas of the face and when 7 months old he was discharged with measles and taken home by his parents. At 9 months he returned to hospital, when his W R. was still strongly positive but his general condition had improved. Dr Still then treated the child with mercury by mouth and by inunction, and at the age of a year he was looking well and the urine was free from albumin. At 18 months the W R. was negative and remained negative for 5½ years, when the patient was last seen at the age of 7 years. He was then apparently well, but none of his permanent teeth had erupted.

The other patient with nephritis who survived was

D K. born in 1935 His father was in the Navy for many years and is said to have suffered only from gonorrhoea. He had no history of a sore and the blood had never been tested until after his child had been brought to Great Ormond Street with frank congenital syphilis. The parents W R. were then both positive, but not strongly so the Kahn reactions were both strongly positive. The child snuffled at birth and at the age of 4 months he attended Dr Sheldon s clinic when the following account of his symptoms was recorded snuffles, peeling hands, erythema on trunk and limbs, condylomata around the anus, palatal ulceration and bleeding gums, café-au-lait colour The child appeared moribund when admitted to the ward. The following day there was marked oedema of the legs and ankles. The urine was albuminous and the deposit contained white and red corpuscles and granular and hyaline casts. On small doses of arsenicals (5 courses of sulphostab " 41 injections = 6·75 G) together with hydrarg c. cret. gr ½ b.d. over a period of 14 months, and with good paediatric attention, particularly during the critical early months of his illness, the child gradually improved and the serological reactions became negative. Snuffles however persisted and adenoid growths appeared which it was deemed expedient to remove when the child was 20 months old. As the nephritis seemed to have cleared after the arsenical and ancillary treatment, the child was given 2 courses of bismuth injections (23 bisoxyl = 35 ml.) when about 2 years of age Subsequently the blood W R. remained negative to the age of

TABLE 8

Case number and sex	Age at diagnosis	Previous symptoms	Symptoms and signs of Nephritis
Fatal Cases			
1 E.H. ♂	3 days	Pemphigus at birth. Rash at 2 days.	Albumin and casts in urine. Urea in C.S.F. 61 mg.
2. G.M. ♀	3 weeks		Oedema of arms and legs. Albuminuria. Blood urea 61 mg.
3 J.H. ♀	4 weeks		Oedema of legs and sacrum.
4 M.H. ♀	4 weeks	Rash and snuffles at 3 weeks.	Swelling of abdomen 4 weeks. Oedema of arms, legs and face 5 weeks. Blood urea 24 mg. at 15 weeks.
5 G.W. ♂	9 weeks		Oedema of legs, ascites, 42 oz. removed by paracentesis
6 D.M.C. ♂	9 weeks, possibly earlier	Hydrocele at 4 weeks. Snuffles at 7 weeks.	Oedema of feet. Albuminuria.
7 J.L.	13 weeks	Green stools 13 weeks.	Oedema of hands and feet. Albuminuria.
8. W.D. ♂	14 weeks	Rash at 10 weeks. X-ray evidence of epiphysitis.	Oedema of scrotum.
9 E.H. ♂	18 weeks		Generalised oedema. Urine contained albumin and clumps of pus cells.
10. A.L. ♂	26 weeks	Enlarged cervical glands, anaemia, hydrocephalus.	Oedema of scrotum and face. Albuminuria. Many epithelial cells. Few pus cells. Later many casts in urine.
Recovered Cases			
11 A.M. ♂	9 weeks	Snuffles at 2 weeks. Diarrhoea and vomiting at 7 weeks. Inability to digest food.	Oedema of hands, legs, lower abdomen and scrotum. Oliguria. Albumin + + many r.b.c. and occasional casts.
12. D.K. ♂	16 weeks	Snuffles at birth. Peeling hands, erythema of skin. Condylomata and palatal ulcer	Oedema of legs and ankles. Urine contained albumin, red and white cells, hyaline and granular casts. Blood urea 20 mg. at 4 months.

Cases of Nephritis

Subsequent development	*Age at death*	*Autopsy findings* (1) *General*	*Autopsy findings* (2) *Microscopic study of kidneys*
	12 days	No sections cut.	
	4 weeks	No P.M.	
Rash and snuffles at 5 weeks.	7 weeks	Changes in liver and spleen. Lesions of the tibiae.	Vessels thickened with interstitial perivascular infiltration. Glomeruli and tubules normal.
Oedema subsided with mercury and arsenical treatment and cleared by 6 weeks. X-ray evidence of epiphysitis 3 weeks. Developed pneumonia and died in 2 days.	20 weeks	Slight changes in liver and spleen. Healing lesions in tibiae.	Glomeruli normal. Tubules, calcinosis, cellular, hyaline and granular casts in collecting tubules. Vessels thickened
	2 weeks	Changes in liver and spleen	Glomeruli normal. Tubules, calcification, cells show swelling and granular change. Vessels thickened.
Patient drowsy while in hospital. Severe anaemia.	11 weeks	Changes in liver and kidneys.	Focal cellular infiltration with mononuclear and eosinophil cells. Vessels, glomeruli and tubules normal.
	18 weeks	P.M. report unsatisfactory	
Snuffles at 16 weeks.	20 weeks	Streptococcal abscess of mediastinum. Kidney changes.	
Hydrocele 20 weeks.	26 weeks	Changes in liver and spleen.	Advanced interstitial nephritis. Shrunken glomeruli. Vessels thickened.
Oedema spread and became more marked. Treated with mercury last 4 weeks of life. Diarrhoea.	30 weeks	Streptococcal abscess of thigh and pelvis. Changes in liver	Glomeruli normal. Vessels normal. Tubular epithelium swollen.
Streptococcal peritonsillar abscess; erysipelas at 9 weeks. Arsenical and mercury treatment. W.R. negative at 7 years—well and W.R. negative.			
Arsenical and mercury treatment. Nephritis cleared by 20 months. Last seen [illegible]. Upper incisor teeth H[1]. Right upper molar Moon. Deaf some years, otherwise well.			

TABLE I

Case number and sex	*Age at diagnosis*	*Previous symptoms*	*Symptoms and signs of Nephritis*
Fatal Cases			
1 E.H. ♂	3 days	Pemphigus at birth. Rash at 2 days.	Albumin and casts in urine. Urea in C.S.F. 61 mg. %
2. G.M. ♀	3 weeks		Oedema of arms and legs. Albuminuria. Blood urea 61 mg. %
3 J.H. ♀	4 weeks		Oedema of legs and sacrum.
4 M.H. ♀	4 weeks	Rash and snuffles at 3 weeks.	Swelling of abdomen 4 weeks. Oedema of arms, legs and face 5 weeks. Blood urea 24 mg. % at 15 weeks.
5. G.W. ♂	9 weeks		Oedema of legs, ascites. 42 oz. removed by paracentesis
6. D.M.C. ♂	9 weeks, possibly earlier	Hydrocele at 4 weeks. Snuffles at 7 weeks.	Oedema of feet. Albuminuria.
7 J.L. ♀	13 weeks	Green stools 13 weeks.	Oedema of hands and feet. Albuminuria.
8 W.D. ♂	14 weeks	Rash at 10 weeks. X ray evidence of epiphysitis.	Oedema of scrotum.
9 E.H. ♂	18 weeks		Generalised oedema. Urine contained albumin and clumps of pus cells.
10. A.L. ♂	26 weeks	Enlarged cervical glands, anaemia, hydrocephalus.	Oedema of scrotum and face. Albuminuria. Many epithelial cells. Few pus cells. Later many casts in urine
Recovered Cases			
11 A.M. ♂	10 weeks	Snuffles at 2 weeks. Diarrhoea and vomiting at 7 weeks. Inability to digest food	Oedema of hands, legs, lower abdomen and scrotum. Oliguria. Albumin +++ many b.c. and occasional casts
12. D.K. ♂	16 weeks	Snuffles at birth. Peeling hands, erythema of skin. *Condylomata and palatal ulcer*	Oedema of legs and ankles. Urine contained albumin red and white cells, hyaline and granular casts. Blood urea 20 mg. % at 4 months.

duction, although unfortunately the laboratory investigations were by modern standards quite inadequate to draw more than the most tentative conclusions It is clear that a glomerular nephritis with widespread capillary damage is not the explanation the clinical picture is not in keeping with such a diagnosis and the absence of any glomerular changes at autopsy excludes it. Lange (1919) reported a case of interest in this respect. His patient, aged 12 weeks, developed oliguria, with haemorrhagic urine, and oedema. Post mortem, the kidney is stated to have shown acute interstitial and parenchymatous nephritis. The symptoms are more suggestive of a glomerular nephritis but the oliguria might have been associated with oedema developing rapidly and the haematuria might have been due to a defect of blood coagulation or a bleeding diathesis such as is sometimes seen in congenital syphilis. The picture of gross oedema suggests rather that it was of a hypoproteinaemic type, but the absence of any plasma protein estimations prevents confirmation. However if it is correct, the deficiency of plasma proteins might be of alimentary origin due to defective ingestion or absorption of hepatic origin due to inadequate synthesis of plasma proteins or renal due to heavy albuminuria This latter condition would be in keeping with the clinical description of the syndrome as a syphilitic nephrosis and the finding of tubular abnormalities is confirmatory however the tubules in three cases were quite normal and the only renal change in these three was an interstitial infiltration. It is possible that this oedema syndrome may be produced in different ways in different patients that in some the disturbance may be primarily renal, whereas in others it may be alimentary or hepatic

In one patient who was under the care of Mr Twistington Higgins in the Hospital for Sick Children (1948) the evidence of renal origin is stronger

H. McL., aged 9 weeks, was admitted to hospital with a history of small vomits during the past 2 days watery stools and being listless. She had a big abdomen since birth, which had become bigger lately She was the second child, the first having died at 7 months of pneumonia. There had been no miscarriages and the parents were said to be well. On examination the abdomen was very distended and there was an umbilical hernia. The liver was very hard and enlarged 2–3 fingers breadth below the costal margin. Ascites and oedema of the lower limbs were present. The clinical diagnosis was portal vein obstruction with ascites and hepatosplenomegaly Seven ounces of clear fluid with high protein content were obtained. The liver was then found down in the right flank and thought to be possibly continuous with a renal or adrenal tumour The urine contained albumin 2% excess of urobilin and showed some granular casts Five days after admission she choked after her morning feed, collapsed and could not be resuscitated. Post mortem, there was marked oedema of the legs and feet. The heart and lungs showed no abnormality The abdomen contained more than 100 ounces of fluid. The liver was much enlarged, very firm and of a pale canary-yellow colour The portal vein and tributaries likewise the vena cava, were found to be patent

so also were the biliary passages. The kidneys were very pale, undifferentiated swollen with congestion of the vessels and pin-point haemorrhages. Various bones showed evidence of syphilitic osteochondritis. Microscopically the glomeruli showed no changes beyond the presence of immature ones under the capsule, which is normal for a child of that age. The vessel walls were moderately thickened and there was a moderate degree of change in the tubular epithelium interstitial cellular infiltration was absent. The kidney lesion was definitely of a nephrotic type. The liver showed intralobular interstitial fibrosis with slight cellular infiltration of the portal canals. The spleen showed marked reduction of lymphatic tissue of the Malpighian corpuscles and considerable engorgement of the sinuses. Syphilis was not suspected during life but the mother's blood tested subsequently gave a strongly positive W R. whereas the father's blood was negative.

This is an instructive case and unique in my experience in that it was thought possibly to have been a renal or adrenal tumour involving the liver Doubtless this tentative diagnosis was associated with the fact that the surgeon under whose care the patient was admitted was particularly interested in renal tumours. To a paediatric physician the association of oedema with a highly albuminous urine would have suggested the possibility of syphilitic nephritis.[1]

Whatever the aetiology of infantile syphilitic nephritis[2] may be and this must remain uncertain until more adequate studies of the biochemical disturbances can be made it is recognized as being one with a very grave prognosis and the high death rate in our group confirms this view The results obtained in cases 11 and 12 do nevertheless indicate that the cautious administration of arsenicals and mercury may reverse the pathological processes and lead to complete recovery Reference has previously been made to cases of syphilitic liver disease (p 169) which did well on the older treatment with arsphenamines and mercury so although it would appear that these drugs are not absolutely contra indicated in syphilitic affections of the liver and kidneys as is sometimes stated the drug of choice in future will be penicillin. This should also serve to prevent the septic complications which may arise in cases of syphilitic nephritis Scully and Yamazaki (1949) reported the successful treatment of one such case with penicillin. Dr Charles Harris, of St. Bartholomew's Hospital, has told me about a similar case which occurred in his practice, and as the case has not been reported the record may be of value

David C was first seen at the age of 4 months. He had a normal birth following the mother's first pregnancy during which she had been well. When 2 days old he had an eye infection which was treated with penicillin. When 11 weeks old his hands swelled suddenly and the swelling had never completely subsided since later it spread to his back and legs. As the mother's and child's W R,

[1] The author is indebted to Mr Twistington Higgins for permission to quote from the clinical record and to Dr Martin Bodian for the account of the autopsy and microscopical findings.

[2] One may mention that in Hochsinger's view (1927 p 141) the treatment of infantile congenital syphilis with the former usual combination of arsenicals and mercury did absolutely no damage to the kidneys "die Nieren absolut nicht schädigen."

were strongly positive the infant was taken to hospital. His urine contained excess of protein and a fair number of red cells; blood urea 40 mg. %. The only other grossly abnormal finding was syphilitic epiphysitis of most long bones by X-rays. The patient was given a 10-day course of 1·2 million units of penicillin by mouth, but as a satisfactory blood level of the drug was not reached in this way the treatment was switched over to intramuscular penicillin, of which he received 1·7 million units in 18 days. His quantitative W.R., which had been positive at 1 in 80, fell to positive at 1 in 20. After an interval he was given a further course of intramuscular penicillin, 1·5 million units over 15 days. His W.R. became negative and it remained negative during the next 6 months, at the end of which time his cerebrospinal fluid was also negative. His Lange curve showed no abnormality; cells disappeared from his urine, as did the protein, and his blood urea fell to 25 mg. %. There was considerable radiological improvement in his bones. He has been followed for the last 1½ years. His W.R. remains negative. He has had no more trouble with his kidneys, but has developed asthma.

(3) Nephritis in older children and adolescents

It has long been known that syphilitic lesions tend ultimately to fibrosis and cicatrisation, as is exemplified by the rhagades around the mouth and the scars of gummata of the liver and other parts of the body. Similarly a generalized diffuse fibrosis may at times be found in the parenchyma of organs such as the liver, kidneys, etc. Still says it has been suggested that cases of chronic interstitial nephritis "which occasionally occur in children and young adults without explanation" may be due to congenital syphilis. Hutinel says that given a case of chronic interstitial nephritis in a young subject, one would scarcely hesitate to suspect a syphilitic origin. To put this matter to the test when the opportunity arose, I began to make investigations upon the possible connection between chronic nephritis and syphilis by doing routine W.R. tests upon children admitted to the wards of the Hospital for Sick Children for chronic nephritis. One of the earliest cases encountered happened to be a patient in Dr. Still's ward, and as it proved to be one of considerable interest, though probably not one of chronic nephritis, a detailed account may not be out of place.

L.K., a girl aged 5½ years, was admitted under the care of Dr. Still in May 1921 with "feverish attacks and trouble with the urine." The father was said to be well. The mother gave no history of any disease but was stated to have had 3 miscarriages, at 4, 5 and 7 months before, and one stillbirth at full term, 4 years after the birth of the patient. The child had no infantile symptoms of syphilis and ailed little until she contracted whooping-cough and measles at 2 years of age. Shortly afterwards the mother noticed that the child was puffy about the eyes. She complained of headaches and did not gain weight regularly. This went on until she was about 5 years old, when fresh symptoms supervened. She had bouts of feverish attacks during which she passed diminished quantities of urine which were mixed with blood. About 14 days before being brought to hospital she vomited twice and the mother noticed that the abdomen was swollen.

On admission to hospital there were some palpable glands in the neck right axilla and both groins. There was no oedema. The urine contained a cloud of albumin, many pus cells, streptococci and no tubercle bacilli. Dr Still remarked that this was evidently a "chronic case" and that the patient's blood pressure should be taken and the eyes examined. The blood pressure was recorded as slightly over 100 mm. of mercury the eyes showed no retinitis or optic neuritis. In a subsequent note (6.v 31) Dr Still remarked that the "history suggests more than a mere chronic interstitial nephritis.

No importance had been attached to the history of the mother's 3 miscarriages and it was not until one had ascertained that the clinical diagnosis was thought to be interstitial nephritis that one took blood for a serological test. The result was not a clear negative and a like result was obtained 15 days later This made one a little suspicious and on reading the family history of 3 miscarriages before and one stillbirth after our patient, suspicion was increased, the more so since the upper central incisor teeth showed H[1] characteristics with slightly converging sides and the 6-year-old molars showed small "tubercles. The mother was accordingly invited to come to the hospital for an interview On going into her history we ascertained that she was married in 1911 when aged 29 and the husband 51 he had been previously married, but had no children. One year after marriage she had a stillborn child at full term. Two years after an 8-months premature baby which lived only 2 hours. The third pregnancy resulted in the patient L.K. About 3 to 4 years later a fourth pregnancy resulted in a stillborn 8-months baby The mother's blood was taken and found to be strongly positive, and as she was 2 months pregnant and there were at that time no facilities for treating expectant mothers at the Children's Hospital she was recommended to a general hospital. Here she was given 5 injections of NAB (1 8 G), between the second and fourth months of pregnancy which gave rise to marked albuminuria. It was noted that the patient was irregular in attendance and that she did not attend after the fourth month. The baby born at 7 months of gestation weighed only 2½ lb and was not seen at the hospital where the mother had been treated. At the age of 3 months she developed bronchopneumonia, for which she was admitted to the Children's Hospital and where she died in a few days. At the autopsy there were small petechiae on the heart. Bronchopneumonia was present. The liver was pale and showed ? miliary gummata in a mottled red area." There was slight perisplenitis and the other organs were said to have shown no abnormalities. Sections were not cut of any of the organs The case was regarded as being one of probable congenital syphilis.'

To revert to the patient L.K., the blood test taken in April 1922, just 11 months after it was originally tested, gave a strong positive W R. which seemed to confirm the suspicion that this supposedly nephritic child was also congenitally syphilitic She was therefore given arsphenamine (5 25 G in 3 courses of 6 injections) and mercury iodide (gr ¼ twice daily). This treatment was well tolerated and at the end of 8 months the W R. was negative. She remained under observation for 7 years until she defaulted at the age of 14. All this time the W R. was negative or nearly negative, and on one occasion when she was 11 years old, and my own laboratory had reported her blood very weakly positive W R. and with a negative Kahn reaction she was tested at another hospital which reported a weakly positive W.R. Kahn doubtful and Sigma 0·75 When 9 years old she was admitted to the ward for spinal fluid and renal efficiency tests. The cerebrospinal fluid was normal the urine showed increased protein no sugar some epithelial cells, few leucocytes, but no casts. The kidneys concentrated 15 G of urea well

It would appear that although the patient was originally considered to be suffering from chronic interstitial nephritis, and on that account we had tested her W R. the later view was that her condition was one of pyuria due to pyelitis. Although, therefore, it does not add to our knowledge of the suggested possible connection between chronic nephritis and congenital syphilis, it is an interesting example of case finding and the fact that the Wassermann test showed at first only slight fixation of complement, and a year later was strongly positive, is in my experience a rare occurrence It shows the importance of following up a weakly positive W R. by inquiring carefully into the patient's history in any case which might conceivably have a syphilitic background.

Grace W., born July 1916 had no infantile symptoms before the age of 3½ months, when marasmus set in She attended hospital for 6 to 8 weeks, then defaulted. Being wartime the child's condition may have been attributed to privation and certainly no blood test was carried out. During childhood she had measles at 18 months, whooping-cough at 2½ years and chickenpox later Shortly before her ninth birthday she had a feverish attack and vomited every day The mother reported that during this time the urine was reddish and yielded a "furry" sediment there was no obvious blood in the urine. The child did not complain of headaches. This continued for 3 months, when the patient was brought to hospital and admitted in Sept. 1925 The mother had been married twice. By the first husband she had 6 ineffectual pregnancies, after which she divorced him. The first pregnancy by her second husband ended in a stillbirth at 8½ months and the patient, Grace was the outcome of the next pregnancy The mother judging by her suggestive teeth was considered to be probably a congenital syphilitic herself On admission the child was pale and thin the urine was of low specific gravity and contained a slight cloud of albumin with a few granular casts the blood pressure was 124/80 The teeth were slightly Hutchinsonian (H[1]). The pupils were unequal, the left bigger than the right the right was "fixed," which the mother said had been the case for 3 or 4 years. The ocular fundi and sensations were normal. The blood W R. was strongly positive. The cerebrospinal fluid was clear contained 22 cells (lymphocytes) per c.mm. and gave a weak W R. and a tabetic type of Lange curve. The results of the biochemical investigations of the blood, carried out by Dr G A. Harrison, were within normal limits, except the blood urea, which was raised to 53 mg per 100 ml. The blood cholesterol was 171 mg. plasma proteins, albumin 6·0 globulins 1 28 the urea concentration was satisfactory The child was treated by Dr Still with mercury iodide pills The urine gradually cleared of albumin and blood, and was normal on patient's discharge from hospital (2.xii.25). One month later the urine was still free from albumin from that time the patient failed to attend hospital again

This was obviously a case of subacute or chronic nephritis probably of several years standing in a child with congenital syphilis but one cannot say that it was one of syphilitic nephritis and it is to be regretted that the patient was lost sight of before she was 10 years old If syphilis did not play a part in the aetiology it is impossible to say what the cause was since there is no mention in the history of any known streptococcal infection, though the condition seems to have started more or less acutely with

vomiting and fever 3 months before the child was brought to hospital. If the condition was a so-called "idiopathic" chronic interstitial nephritis, the outcome of an infantile nephritis which the patient had survived one would not expect antispecific treatment to benefit the patient. If on the other hand the nephritis was a subacute recrudescence of an earlier syphilitic condition or even one of ordinary aetiology in a syphilitic patient improvement might be expected to follow antisyphilitic treatment, but it would be desirable in such a case to put the patient upon a nephritis regimen and diet before instituting antisyphilitic treatment.

The next case of nephritis in an older child was that of a patient, Peggy D., who had a rash in infancy for which she was treated with mercury for an unspecified time. At the age of 6 months she was an inpatient in another hospital on account of trouble (? epiphysitis) in the left elbow. At 9 years she had arthritis of both knees, for which she attended yet a third hospital, where she was given no antispecific treatment. At 10 years of age she had interstitial keratitis of the left eye, for which she was given injections at an ophthalmic hospital. At the age of 11 years she attended the Children's Hospital and as her blood W. R. was still strongly positive she was given treatment with arsphenamine and mercury iodide pills. This was in the latter part of 1931 and as we had until then never seen a case of nephritis in a child which seemed to be attributable to arsphenamine injections, we did not as a matter of routine examine the urine before each injection. During the third course of neo-arsphenamine and mercury iodide (after having received 16 NAB = 6·3 G.) the patient complained of colicky pains in the abdomen, with vomiting and diarrhoea, and 2 days later the abdomen became enlarged. The child was admitted to the ward, where she was found to have ascites and oedema of the legs; the blood pressure was not raised; the urine was reduced in quantity, contained few red blood corpuscles and was "solid" with albumin. The blood urea was 41 mg. (16.11.32) and the blood cholesterol 280 mg. (17.III.32). Six weeks after admission the urinary output suddenly shot up from 20 oz. to 50 oz. (0·5 to 1·4 litres) in the 24 hours, and this improvement was maintained. On discharge to a convalescent hospital there was no oedema, albuminuria was 0·15% and the blood pressure was normal, as it had been throughout her stay in hospital. Appetite and diet were normal. The clinical diagnosis was "parenchymatous nephritis," though whether this was the result of the treatment with heavy metals or a true syphilitic nephritis or nephrosis it is impossible to say. Ten months later as the patient seemed very well and the urine was clear and free of albumin, arsphenamine injections were resumed and although there was no recurrence of the renal troubles, the patient did not take kindly to the treatment, for on one occasion she had a rigor after 0·3 G. N.A.B., she was sick on several occasions after the intravenous injections and once she had a headache and was sick in the evening after an intramuscular injection of sulphostab in the afternoon. Yet with all these signs of intolerance she had no return of albuminuria.

In this case the nephritis may have been syphilitic in origin or due to the arsphenamine treatment or possibly to a more ordinary cause in a patient suffering from congenital syphilis. Urinary manifestations, albuminuria and cylindruria, may undoubtedly follow upon bismuth medication as will be described later (p. 431). We recorded these manifestations in 50 out of 260 patients (19 per cent) thus treated. Only

twice however was the pathological condition sufficiently pronounced to justify it being called a bismuth nephritis and in neither case was the kidney damage permanent

Lange (1919) stated that his observations did not disclose any cases of kidney damage resulting from treatment, nor could he say if mercury treatment was the cause of nephritis in any case. On the other hand, Hutinel was of the opinion that mercury especially in the form of unguentum hydrarg when used in the treatment of neonatal syphilis might give rise to renal damage. It remains to be seen if under the modern methods of treatment syphilitic nephritis in early infancy will become less frequent than in the past.

Orthostatic or postural albuminuria in later childhood and adolescence has been attributed, among other causes, to congenital syphilis. Hochsinger and Hutinel mention that it is a common occurrence at this period, the former quoting Stuempke, who found it in 6 out of 46 cases, and Arnold in 70 per cent of all the older congenital syphilitics. Hutinel correlates the condition which he names orthostatism, with the physical maldevelopment of the congenital syphilitic patient, who is often tall, has a certain *gaucherie* in walking and defective circulation giving rise to what he calls *acrocyanosis of the extremities* Orthostatic albuminuria and acrocyanosis, the two symptoms of orthostatism, he attributes to some derangement of the vagosympathetic nervous system. Lordosis has been shown to be an important contributory cause. Saito (1921) on the other hand dismisses congenital syphilis as a cause of orthostatic albuminuria, and our own observations point to a similar conclusion.

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(*d*) *The Pancreas*

The pancreas is affected with the other organs and tissues of the syphilitic foetus and neonate Hoffmann has figured the *T pallidum* swarming in the blood vessels and in the young perivascular connective tissue between

BONES AND JOINTS

Historical

The bone lesions in syphilitic foetuses and neonates are so characteristic and widely distributed in the body that they received a considerable amount of attention from clinicians and pathologists during the latter half of the last century The discovery of X rays in 1895 and of the *Treponema pallidum* 10 years later opened up a new vista in the study of this aspect of congenital syphilis, and investigators of many nationalities interested themselves in the subject.

It has already been mentioned that the early observers Rosen von Rosenstein, Bertin and others, referred to bone lesions in early congenital syphilis yet later writers, among them Trousseau (1847), Diday (1854) and Lancereaux (1868) considered the bone affections to be a rare manifestation of the disease. These divergent views were doubtless due to the fact that rickets and congenital syphilis were often present in the same individual, and that the osseous lesions of the two diseases were coexistent and were hence confused. In 1870 however with the publication of Wegner s classical account of the bone lesions in congenital syphilis, to which he gave the name *osteochondritis syphilitica* the condition was placed on a firm pathological basis. Wegner s conception of the lesion as the name osteochondritis implies was of its inflammatory nature and he described three stages of the pathological process.

In point of time Wegner was closely followed by Parrot who recorded his clinical and pathological studies in 1871 and 1873 and who may be considered the pioneer in establishing osteochondritis as a definite syndrome (McLean). His original description of the clinical condition, now universally known as Parrot s pseudoparalysis, has left little to be added by subsequent writers He emphasized the participation of the periosteum and perichondrium in the histopathology of the lesions and he disagreed with Wegner s theory of the inflammatory nature of the cartilaginous and bony changes. Parrot regarded them rather as the results of a nutritional disturbance of the osseous tissue at the site of ossification—a syphilitic dystrophy He established the fifth month of intra uterine life as the earliest time for the appearance of the lesions, and he was also the first to state that they affected practically every bone in the body Wegner s and Parrot s pioneer observations were speedily followed by reports of cases by observers in many countries. In 1872 appeared the first American report by Curtis-Smith of a case of syphilitic dactylitis and in 1875 R. W Taylor also in America, published a monograph in which he reported 12 personal cases of syphilitic lesions of the bones.

In Britain cases were shown at the Pathological Society of London and or reported by Haward Macnamara, Barlow Parker and others

while on the Continent the pathologists Waldeyer and Köbner Heubner and the clinicians Poncet, Henoch, Kassowitz and Hochsinger all made contributions to our knowledge of the subject (McLean)

Barlow then a rising young physician, was impressed by Parrot s work and piloted British medicine in a series of papers (1876–80) upon congenital syphilis and its allies (rickets, craniotabes) into following the French school of thought as regards the pathology of the bone lesions in these conditions. Barlow agreed with Parrot that the syphilitic bone lesions were due to an altered pattern of nutrition rather than to an inflammation, which the German school, following Wegner Virchow and others,

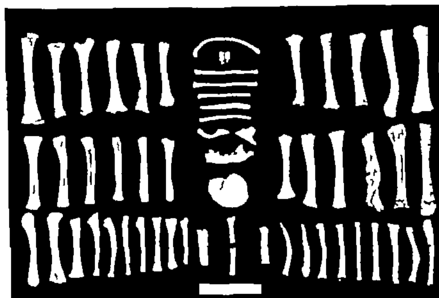


Fig 61 Collection of foetal syphilitic bones presented to the Museum f the Hospital for Sick Children, London, by Dr J Parrot, 1879

held to be the case. In 1880 Barlow (7) stated that separation of the epiphyses which several observers had reported to occur in severe cases of syphilitic bone disease, did not result from actual *suppuration* in the softened osseous bone, although true suppuration did occasionally occur in the structures surrounding the end of the bone.

Between 1900 and 1904, Hochsinger wrote various articles dealing with the X ray appearances of the bones in congenital syphilis, and in 1904 he published an important monograph upon the subject in which were embodied the correlated results of his clinical, radiological and anatomical investigations upon syphilitic foetuses and infants. He confirmed Parrot s observation that all syphilitic foetuses of viable age showed microscopical evidence of osteochondritis

During the first decade of this century various Continental radiologists and paediatric pathologists devoted themselves to the study of the problem. Among them Oluf Thomsen (1907) did important work in this field. He was the first to emphasize the importance of X rays in the diagnosis of congenital syphilis in the newborn apparently healthy infant. He found bone lesions in 86 per cent of 142 cases. He regarded the periosteum as the source of the soft granulation tissue which resulted in separation of the epiphysis and he stated that this type of periostitis was always an antenatal condition, whereas the affection of the membrane bones, as, for example, periostitis of the skull was always postnatal.

The demonstration by Levaditi and Sauvage in 1905 of the treponema in the bone marrow stimulated similar researches by other investigators—Bertarelli and Volpino (1906) Hoffmann (1908) Thomsen (1912) and many others—who were able to confirm Levaditi's original observations. These researches showed that the treponema has a great affinity for the bone forming tissues of the foetus, particularly at the epiphyseal ends of the long bones where bone growth is most active. Here the treponema can be seen, in suitably stained foetal or neonatal bone, in the marrow spaces of the cartilage, in the zones of ossification and in the deeper layers of the perichondrium and periosteum (Schmidt) Schneider[1] showed that the treponema bored its way into the bone corpuscles and could be seen in them after it had disappeared from all the other osseous structures. This doubtless explains the frequency of bone recurrences met with in late congenital syphilis

Investigators in several countries made radiological observations which added materially to our knowledge. Fraenkel (1911) Alexander (1915) Wimberger (1925) and Engel and Schmidt (1928) may be mentioned among the German authorities. Wimberger correlated the known pathological lesions of rickets, scurvy and congenital syphilis with his own X ray observations. He confirmed Parrot's observation that the earliest involvement of the skeleton occurred at the fifth or sixth month of foetal life, and that the maximum changes were seen in the first few months after birth subsiding rapidly from the sixth month onwards. He drew attention to the areas of rarefaction due to softening, which may be seen in many of the long bones and notably at the upper and inner aspect of the tibiae. This has since been called Wimberger's sign though it had been observed several years previously at Great Ormond Street, where it was known as the cat bite lesion of the tibia. Other investigators who made similar radiological studies include Shipley and his collaborators in America (1921), Péhu and collaborators in France (1924–27) and de Jong Martis in Indonesia (1937). The last named in Java found bone

[1] Schmidt and Schneider both gave detailed descriptions of the microscopical changes seen in the bones in congenital syphilis A good account will be found in McLean's first article 1931 pp 144–148

lesions in 94 out of 100 syphilitic Indonesian and Chinese infants 59 of them between 6 weeks and 3 months and 35 more than 3 months old

Among British pathologists, Turnbull (1916) Harris (1933) and Gilmour (1940, 1944) have made important contributions to our knowledge of syphilitic bone lesions. In the report by Holland previously quoted (p 62) on the causation of foetal death, Turnbull has given an authoritative account of the changes observed. The commonest situation is in the metaphysis—the part of the diaphysis adjacent to the epiphysis—and in the epiphysis itself the combination of metaphysitis and epiphysitis constituting Wegner's *osteochondritis syphilitica* Less commonly inflammation may occur in other parts of the diaphysis and/or in the periosteum.

(1) **Syphilitic osteochondritis.** The effect of syphilitic osteochondritis upon the normal zones is manifold, varying as it does with (*a*) the degree of injury to the tissues by the treponema and its toxins, (*b*) the intensity and stage of the inflammatory reaction, and (*c*) the site, in cartilage or metaphysis of the maximum of injury and inflammatory reaction. The resulting macroscopic and microscopic appearances are described by Turnbull as follows

1 The yellow zone of provisional calcification, normally not greater than 0 5 mm. deepens to as much as 2 mm. or more This is brought about by the continued growth in length of the cartilage and by the continuance of the normal changes in it which, including calcification, are preparatory to its transformation into bone. All this time invasion from the diaphysis of the provisionally-calcified cartilage by vessels, osteoblasts and osteoclasts may be checked. In early lesions the junction of epiphysis and diaphysis remains regular and unbroken.

2 Whilst ossification from the diaphysis is checked in this manner in most of the epiphyseal-diaphyseal junction, it may continue at the sides of one or more of the vertical vessels which unite the cartilage and the diaphysis. At such spots the deep zone of provisional calcification becomes shallow and consequently the diaphyseal border of the zone is notched and irregular

3 Interference with the blood supply may lead to the degeneration of the epiphyseal cartilage so that parts of it do not undergo provisional calcification and subsequent ossification The vertical vessels which unite the cartilage with the diaphysis are relatively large vessels and the blood supply from these is less likely to be cut off Provisional calcification and subsequent ossification usually proceed, therefore round some at any rate of these In consequence, narrow processes or broader tongues of red marrow project from the diaphysis into the epiphyseal cartilage and alternate with tongues of cartilage which project into the diaphysis This gives rise to the saw tooth metaphysis, the zone of provisional calcification following the irregular line of the interlocking teeth

4 Fibrosis is seen with the microscope in all but the slightest and

earliest lesions. It may affect the marrow of the metaphysis, or of the canals in the cartilage, or of both. In advanced, intense inflammations a *dense granulation tissue is formed*, which in the metaphysis is associated with erosion by osteoclasts of trabeculae of calcified cartilage and bone. When the cartilaginous canals are affected they become greatly widened. The granulation tissue may caseate and soften, which may lead to separation of epiphysis from metaphysis, or the epiphysial cartilage may be divided completely at a short distance from the epiphysial–diaphysial junction.

Fibrosis is of the greatest assistance in the *microscopic* and *macroscopic* recognition of syphilitic osteochondritis. When slight fibrosis is present in the metaphysis, the marrow in the metaphysis appears to the naked eye more compact and paler than in the remainder of the diaphysis. *The affected metaphysis still feels gritty when tested with the point of a scalpel.* It may be pink or grey; it is frequently yellowish owing to the presence of numerous yellow trabeculae of calcified cartilage in a grey *fibrous matrix. The contrast with the remainder of the diaphysis is* accentuated when the *bone has* been placed *for a few minutes in formaldehyde*. More advanced fibrosis appears slaty-grey or yellowish, gelatinous and slightly bulged and feels soft owing to the erosion of calcified cartilage and bone. When slight fibrosis is present in the epiphysial cartilage the vascular canals are more conspicuous than normal. When advanced fibrosis is present pink, grey or yellowish strands interrupt the cartilage in the sites of the canals.

Turnbull summarizes the possible changes in the normal pattern of the epiphysial–metaphysial junction as follows: deepening of the zone of provisional calcification; irregularity of the line of junction between the epiphysis and diaphysis; multiple zones of provisional calcification; enlargement of the chondral vascular canals; fibrosis in the marrow of the metaphysis or of the canals of the epiphysial cartilage."

Differentiation of syphilitic osteochondritis from rickets. Like syphilis rickets also gives rise to irregularity of the epiphysial line as well as to enlargement of the cartilage canals, *but in this case the essential abnormality is absence of calcification.* Provisional calcification of the epiphysial cartilage ceases and moreover all bone formed during the disease remains "osteoid" that is to say does not become calcified after its deposition. In the metaphysis of the long bones a zone of *closely packed, osteoid* tissue is formed. This is frequently yellowish in colour but when tested with the point of a needle or knife it is found to be tough, elastic and free from grit, whilst the yellow deepened zone of provisional calcification in syphilis is hard and gritty. Further all the bone becomes soft owing to the formation of osteoid tissue, whilst the old, true bone is removed in the process of growth. The whole bone, therefore, is cut with the knife with abnormal ease and in later stages the bone is pliable. In syphilis

there is no such softening except in areas of fibrosis accompanied by erosion of bone. Such areas are focal and the granulation tissue therein can be recognized with the naked eye the remainder of the bone remains hard and brittle. (Turnbull.)

(2) **Syphilitic diaphysitis.** Areas of syphilitic inflammation are frequently seen in the medulla of the diaphysis distant from the metaphysis. They are variously named by authors diaphysitis osteitis and osteomyelitis. Turnbull states The fibrosis is associated first with cessation of the deposit of bone, and later with erosion of the trabeculae of bone and calcified cartilage present. In early stages the areas of fibrosis are seen by the naked eye as paler pink areas in the red marrow of the diaphysis in later stages the granulation tissue is slaty blue or yellowish, frequently gelatinous, and the affected area feels soft.

(3) **Syphilitic periostitis.** This lesion is rare but may accompany *advanced osteochondritis. It results in* a layer of bone and red marrow or rarely granulation tissue, being deposited outside the original corticalis. This periosteal cloaking can be easily recognized macroscopically It is not diagnostic of syphilis, for in rickets a similar zone of marrow and osteoid tissue may be formed outside the original cortex.

In conclusion says Turnbull, congenital syphilitic disease of bone is not a general systemic condition, but is due to the local presence of tre ponemata. The older the child the fewer are the portions of bone affected In the foetus the infection tends to be widespread but it is not necessarily universal. Further when several bones are affected the lesions are greater and more conspicuous in some bones than in others. It is advisable, therefore, in each case, to examine as many bones as possible. The femur tibia, humerus and ribs are sites of election the femur and ribs are easy of access and should certainly be examined in all cases.

McLean (1931) published a monograph on what is probably the most comprehensive investigation of the osseous lesions in infantile congenital syphilis that has ever been undertaken. The investigation was carried out *in New York between the years 1923 and 1930 and included the correlation* of the clinical picture of the disease with the X ray photographs, and the macroscopic and microscopic examination of the pathological material furnished by the 102 patients studied and the 24 autopsies of those who died. The monograph starts with a full historical survey of the work carried out by previous investigators, a survey which will prove to be of great value to any student of the subject. I personally am indebted to McLean s monograph for much of the information given in the historical portion at the beginning of this chapter as well as for the description of the lesions as detailed and figured by him.

Of the 102 patients comprising the study 73 were in the first trimester and 19 in the second so that 92 of the total number 90·2 per cent, were aged 6 months or less when they were first investigated. The death rate

in the first, second and third months of life was 54 5 52·8 and 34·6 per cent respectively or during the 3 months from birth onwards 46 5 per cent. The first 3 months are to be regarded as the period of election for all varieties of lesions, and the first 6 months as the age of election for osteochondritis (epiphysitis). These, he says, might be termed specific lesions. Lesions occurring during the second half of the first year are largely of the residual variety such as periosteal cloaking changes in trabeculation and the like.

Clinically the cases could be divided into severe (57) moderate (28) and masked or latent (17), the last group being diagnosed by X ray examination and by doing routine blood tests. Only 33 of the patients, or just under one third, had clinical signs of bone involvement.

Prematurity Prematurity seemed to have a definite influence on the bony lesions. Clinical manifestations were of the florid type in 10 patients, moderate in 2 in only 6 of the 12 cases were the osseous lesions severe, yet 10 of the 12 patients died. There seemed to be a definite tendency in premature syphilitic infants during the first 2 months of life to show by X ray deep zones of submetaphysial rarefaction which microscopically were found to be caused by extreme lawlessness of growth with unusual production of connective tissue. McLean was of the opinion that the rapid growth in length of many premature infants was the probable explanation of these deep zones of submetaphysial rarefaction, quite apart from any syphilitic lesions.

Arthritis Arthritis of a purulent character due to infection by pyogenic organisms occurred in 4 of McLean s cases (4 per cent).

Anaemia. Anaemia is probably not to be regarded as having an aetiological relationship with the osseous lesions, as the background of both these manifestations is doubtless the treponemal infection. It is, however recognized that any severe anaemia in infancy if of long standing, may show radiological changes in the long bones, and severe pyogenic infections may also be accompanied by bone changes, possibly on account of the associated anaemia. Severe anaemia in congenital syphilis is usually associated with marked osseous lesions (see p 238)

The osseous lesions. Osteochondritis (epiphysitis) was present in 90 per cent, periostitis in 70·6 per cent and osteomyelitis in 46 per cent. The tibia and ulna were the bones most frequently involved (97 per cent) the radius coming next with 91·3 per cent In terms of the growing ends of the bones, it was noted that the distal ends of the radius and ulna were the metaphyses most frequently affected. Lastly McLean found that if the metaphysial lesions and the diaphysial osteomyelitic lesions of the upper end of the tibia are grouped together the combined incidence is 77 per cent, which is greater than in any other lesion In addition to the changes in the long bones occasional living infants showed X ray lesions in the following bones bodies of the lumbar vertebrae, clavicle, acromion and

coracoid processes of the scapula ribs, ilium, tarsal bones, metacarpals phalanges and skull. In his earlier cases McLean attempted to assess the changes in the skull bones, but he soon abandoned the project, as the plates were so difficult to interpret.

Periostitis *alone* was found in only 5 of the cases, aged 10 weeks, 5 5 11 and 13 months respectively The fact that only one of the patients was less than 5 months old shows the rarity of this type of lesion as an isolated observation at the age when the X ray diagnosis of congenital syphilis is most valuable Rachitic and syphilitic lesions were present simultaneously in at least 8 of the cases, and possibly more frequently

(*A*) *Osteochondritis* This is the most frequent lesion in infantile congenital syphilis. Its site is at the junction of the metaphysis and epiphyseal cartilage, hence it is also known as epiphysitis or metaphysitis All authors are agreed that in syphilitic foetuses and in syphilitic infants during the first few weeks of life, there is (1) a deepening (widening) of the provisional zone of calcification of the long bones, seen in X ray negatives as a white cap on the diaphysis, and in the print as a dark metaphyseal band. This metaphyseal (or diaphyseal) cap if present alone, can only be regarded as suggestive, but not conclusive, of congenital syphilis. If in addition to metaphyseal capping, there occurs (2) submetaphyseal rarefaction and (3) loss of bone cortex at the upper and inner aspect of the tibia, the appearances are pathognomonic for congenital syphilis. (4) The zigzag appearance of the metaphysio-epiphyseal line, the saw tooth edge, McLean regarded as the first evidence of lawlessness of growth, which is so characteristic of the active stage of osseous syphilis. There is a disruption of the adjustment normally present in rapidly growing bone. According to him the cause of the saw tooth metaphysis is a local circulatory disturbance which, if prolonged, always gives rise to the formation of connective tissue and excessive resorption of bone. (5) The next sign is a variable amount of submetaphyseal rarefaction, with or without a deepened provisional zone of calcification.

McLean s summary of the pathology of osteochondritis is as follows

Osteogenic injury is manifested by diminished osteoblastic activity alteration in the growth of cartilage, and disturbance of normal resorption. There result (*a*) an excess of calcified intercellular ground-substance which piles up at the metaphysis, and (*b*) deficient subchondral trabecular formation These changes initiate abnormal resorption and eventually the production of connective tissue. Coincident with its appearance lawlessness of growth becomes apparent, and excessive osteoclastic activity becomes manifest with the resorption of varying portions of the metaphyses and diaphyses, which explains the various X ray pictures of syphilitic osteochondritis" (p 392).

(*B*) *Osteomyelitis and ostitis.* Osteomyelitis and osteitis as shown by resorption of various parts of the ends of the bones, as well as of the shaft

and cortex may also occur Replacement by connective tissue and the formation of new bone at the end of the metaphysis as well as along the shaft and the periosteum (periosteal cloaking) are later manifestations of the bone lesions In some cases the bones of the hands and feet (carpal, metacarpal, tarsal and metatarsal) may show rarefaction and enlargement. Occasionally the ends of the long bones may be so enlarged as to simulate rickets.

Dactylitis was rarely found to occur in the first months of life, except in association with involvement of the long bones of the extremities. McLean could give no statistics for this condition since the patients hands and feet were held by an assistant flat against the plate so as to *obtain the best possible X ray pictures of the long bones of the limbs*

Epiphysial separation as seen by X ray is usually a break at the end of the diaphysis, the smaller fragment remaining attached to the epiphysial cartilage. *This separated epiphysis may often be impacted—sometimes* out of alignment with the shaft of the bone. Only rarely is a true epiphysial *separation seen by X ray*

(C) *Periostitis* Periostitis is rarely seen as the *only* lesion present hence it has not the diagnostic significance of osteochondritis which often occurs without periostitis. The periosteal lesion may be of three types (*a*) periosteal thickening of an intact shaft independent of lesions at the metaphysis, and usually thickest in the middle of the shaft (*b*) a supportive or healing type found over a break in the cortex the periostitis callosa of Schneider which is usually thickest at the ends of the bones and (*c*) ossifying periostitis or the hypertrophic osteoporosis of Pehu, which is the least common of the three. It occurs in the form of great thickening of the entire shaft due to a series of enveloping coat like layers of newly formed bone. McLean did not observe this type before the fourth month of life the other two types were common at an earlier age. Multi layered periosteal cloaking may be present as the predominating lesion after the fourth month and as the *sole active lesion after the fifth month* of life. At this age and up to the early part of the second year it is of great diagnostic importance.

It should be noted that some of the periosteal lesions were not unlike those of rickets, and a healing severe rickets may resemble syphilitic periostitis.

The types of X ray lesion upon which a definite diagnosis of congenital syphilis may be made in the early months of life McLean gives as follows

(1) Well-defined saw-tooth metaphyses in well-calcified bones.
(2) Deep zones of submetaphysial rarefaction.
(3) Multiple separation of epiphyses, with or without impaction in bones which are not rachitic.

(4) Bilateral symmetrical osteomyelitis of the upper mesial aspects of the tibiae.
(5) Multiple circumscribed osteomyelitis of the long bones shown radiologically as patchy areas of rarefaction.
(6) Multiple longitudinal areas of rarefaction in the shafts of the long bones, sometimes resulting in fractures.
(7) Foci of rarefaction at the mesial or lateral aspects of the metaphyses
(8) Multiple areas of cortical destruction generally seen within a centimetre of the ends of the bones.
(9) Localized periosteal cloaking occurring in more than one bone.

He gave it as his opinion that syphilitic lesions were always distributed bilaterally and in the first months of life the lesion of a single bone was never found to be due to syphilis.

Lastly McLean concluded that X rays were of outstanding importance in the diagnosis of congenital syphilis in early life, since all of the 102 infants he examined had radiological evidence of osseous lesions. Our own observations, to be given later while in the main confirming McLean's opinions and results, do not entirely agree with his, for we obtained X ray evidence of osseous lesions in only about 85 per cent of our patients, and in at least one patient it appeared as if the syphilitic lesion affected a single bone (see p 200)

Harris in his monograph (1933) gives the results of his investigations upon the growth of bones in health and in disease. He agrees with Wegner Turnbull and others that the process is a chronic inflammation occurring in the zone of proliferation and provisional calcification of the cartilage. Lymphocytes infiltrate the zone of inflammation, and healing is effected by the deposition of fibrous tissue ranged transversely This abnormal arrangement of the fibrous tissue explains the irregularity in the trabeculation of the bones which can be detected with a lens in X ray negatives of healed infantile syphilitic lesions.

Personal Observations

Having given a brief survey of the history of the bone lesions in early congenital syphilis and an account of Turnbull's, McLean's and Harris's contributions to our knowledge of the subject, it remains now to integrate our own experiences with those of previous workers, at the same time illustrating the various phases of the osseous lesions by examples from our own patients.

Incidence and prognosis

Of 244 syphilitic infants below the age of 12 months, 151 (62 per cent) were found to be clinically free from any sign or symptom of epiphysitis

and 93 (38 per cent) were clinically positive. Of the 151 who were clinically *negative 102 were examined radiologically* with the result that 78 showed X ray evidence of osseous lesions, whereas 24 were negative From these data it was calculated that the *incidence of syphilitic bone disease* among our infantile cases was about 85 per cent. Table 9 gives the numbers in relation to the age period and the deaths among 165 of our patients As was to be expected the prognosis was worst in the youngest patients. Very few of our infants were less than 1 month old when we first saw them, but at that age the mortality from congenital syphilis was more than 50 per cent at the time of which I am writing, *1917 to 1939 Most of the deaths not directly due to syphilis (column 5)* were from gastro-enteritis, bronchopneumonia or whooping-cough, but the syphilis might have shared with these complications the responsibility for the fatal outcome.

TABLE 9

Investigation of 165 Patients with Clinical and/or Radiological Epiphysitis in Relation to Age-period and Fatal Outcome

Age-period	*No. of patients*	*Total deaths*	*Deaths directly due to syphilis*	*Deaths not directly due to syphilis*
0–3 months	1 0	42 = 38%	27 = 24 5	15 = 13·5
3–6 months	46	9 = 9·5 %	9 = 19·5	0 = 0%
6–12 months	9	2 = 22%	1 = 11%	1 = 1
Total 0–12 months	165	53 = 32·1 %	37 = 22 4	16 = 9 7

Our finding of 78 patients with X ray evidence of epiphysitis among 102 who were clinically negative as regards bone lesions shows the importance of taking X ray photographs of all infants suspected of being congenital syphilitics or who may be thought to be suffering from a bone or joint lesion. For many years it was our practice to X *ray all four limbs of our* syphilitic patients and we did not as a rule X ray the head, ribs or clavicles *for although changes might* have been detected in them, the cost and trouble involved would not have been justified except as part of a special investigation, since a diagnosis could always be made from an examination of the limbs alone.

Severely infected foetuses and infants usually die, but when, as frequently happens, *the infant is apparently healthy at birth and the disease* manifests itself after the usual incubation period of 3 to 6 weeks, the *osseous lesions, however generalized or severe* they may appear by X ray usually clear up by the end of the first year of life There may however be two possible sequelae (1) a liability to a recurrence of bone lesions, the periostitis and osteitis of *late* congenital syphilis, and (2) a liability to

fractures, due perhaps to an alteration in the trabeculation of the long bones.

Clinical manifestations of syphilitic epiphysitis

It is important to bear in mind that it is the exception rather than the rule for a patient with congenital syphilis to show clinical evidence of epiphysitis of every 100 of our patients 62 had no *clinical* epiphysitis whereas only 38 were clinically positive. *Radiologically* however 85 per cent of our patients showed evidence of bone lesions. Syphilitic bone lesions may occur during the later months of gestation and be present at birth, or on the other hand they may not become apparent until the sixth or eighth week of life or even a little later It is important to remember that a negative radiological result from the bones at 4 to 6 weeks of age or a negative blood test does not necessarily imply immunity from syphilitic epiphysitis, as the following cases show

Alan H., born August 1933 developed gonorrhoeal ophthalmia shortly after birth. While in hospital for the treatment of his eye condition he started to snuffle at the age of 5 weeks. Mother and child gave a positive W R. There was no clinical or radiological evidence of epiphysitis. Four weeks later however pseudo-paralysis of the right arm appeared, with radiological evidence of syphilitic bone disease in the tibiae and the right forearm. The lesions had cleared before the child was 6 months old.

Emily S. born Dec. 1927 to a known syphilitic mother who however had never been treated, had no symptoms of congenital syphilis and a negative W R at the age of 5½ weeks. At 14 weeks the right leg became painful and tender and the child had some rhinitis accompanied by snuffling The W R. was now strongly positive and radiologically periostitis of the right tibia was apparent. The child was given 2 courses of sulphostab (1 175 G) and mercury The periostitis of the tibia became more marked before it subsided at the age of 7½ months. The W.R. was positive once only and subsequently was negative on 11 occasions to the age of $7^{10}/_{12}$ years.

Epiphysitis is usually symmetrical, but a joint in one limb may be more severely affected than its fellow in the opposite limb. Frequently many joints are involved. They are obviously painful and/or tender for the infant cries when the joints are moved either actively or passively When the upper limbs are affected the joints are flaccid and when the arms are held up and then released, they fall helplessly on the bed as though paralysed. It was on that account that Parrot called the condition "pseudo-paralysis," since he was convinced it was not a true paralysis resulting from a central or peripheral nerve lesion When the shoulder is involved, as is often the case in a supposed birth injury the arm hangs by the side, the elbow is turned out, the palm of the hand points backwards and outwards and the condition suggests Erb's paralysis (Carpenter) When epiphysitis attacks the lower limbs the condition is one of spasticity

and the legs are held in a stiffened attitude of flexion We had several cases in which the clinical diagnosis was ? a birth injury ? Erb s paralysis, but in which radiologically syphilitic epiphysitis was found The following is an illustrative history of such a case

Joyce G was born Nov 1930 as a breech presentation by which the arms were thought to have been injured. The right arm was "paralysed" from birth, and when at the age of three weeks the infant was examined at the Surgical Out patients Clinic the right arm was flaccid but the infant moved its fingers. The surgeon s diagnosis was ? Erb s paralysis. An X-ray of the shoulder revealed osteoperiostitis of the humerus. The child snuffled from birth and later developed a stridor and increasing difficulty of respiration, for which she was admitted to a medical ward and found to be suffering from bronchopneumonia. When exactly three months old the other arm became flaccid and an X ray of that arm showed a fracture at the upper end of the humerus. In the mean time the W R. had been found positive thus confirming the X ray diagnosis of syphilitic epiphysitis of the right arm. The child died at the age of 13 weeks and an X ray taken after death showed well marked osteoperiostitis of the femora and tibiae. There was also separation of the upper epiphysis of the left humerus.

The cause of Parrot s pseudo-paralysis is still a matter for conjecture. The most widely held view is that it is due to pain which prevents the infant moving its limbs by some it is thought to be of central origin while Hochsinger was of the opinion that it was due to an affection, perhaps involving their nerve-endings, of the muscles serving the joint. Whatever the causation may be, the paralysis responds readily to antisyphilitic treatment. Local treatment such as the application of splints or plaster bandages, is rarely if ever required

Other infantile diseases which syphilitic epiphysitis may simulate are coccogenic osteomyelitis, rickets scurvy infantile paralysis and erythroblastosis foetalis. Examples of some of these conditions may be cited from our experience

(a) Coccogenic osteomyelitis

Harry G born May 1933 had no infantile symptoms of congenital syphilis until at the age of 9 weeks there was a marked swelling and tenderness of the right leg below the knee The child was not obviously ill, with only slight fever (99 to 100 F), W B C 10,500 per c.mm. blood culture sterile Mantoux negative. The X ray showed well marked signs of osteoperiostitis and osteitis of the upper half of the right tibia, with the loss of cortex which I had then come to regard as diagnostic of congenital syphilis. My colleague Mr Twistington Higgins, under whose care the patient was, allowed himself to be persuaded albeit unwillingly not to operate upon the patient. Two later X rays, taken 6 and 12 days after the first, showed an extension of the lesion down the tibial diaphysis, and this tibia was still the only bone to be apparently affected. A W R. taken at 11 weeks was positive but not strongly so the titre may have been rising or falling As a compromise the patient was treated with mercury by mouth and inunction The child s general condition was not deteriorating the

leucocyte count was 8,000 per c.mm. and by X-ray 4 weeks from the start some improvement seemed to have set in. A week later the child was well enough to be sent home. Unfortunately the infant developed gastro-enteritis and had to be readmitted to hospital 3 days after having left it, and he died within 2 days. Post mortem, the right tibia showed signs of healing with marked cloaking of the periosteum. The left tibia was normal (Fig 62).

This was an instructive yet difficult case. The fact that only a single bone was affected should have been strongly in favour of coccogenic osteomyelitis and against syphilis. McLean, it will be remembered, stated that he had never seen an infantile case of syphilitic disease in which only one bone of the skeleton was affected. The absence of leucocytosis was against coccogenic osteomyelitis, so also was the good general condition of the patient.



FIG 62 Syphilitic myelo-osteoperiostitis in a child of 11 weeks diagnosed clinically as a ? coccal osteomyelitis. This was the only sign of congenital syphilis and apparently the only long bone affected It shows the characteristic "cat-bite" lesion with loss of cortex and marked supportive periostitis of the upper two-third of the tibia

(*b*) *Rickets* The possible relation between rickets and congenital syphilis will be considered later (p. 212) The differences in the microscopic appearances described by Turnbull have been given on p 192. Fig 63 shows the X ray appearances of a case in which the two diseases were thought to coexist in the same patient.

Jean M. born Mar 1928 to a mother who was later shown to be herself a congenital syphilitic, is stated to have cried from birth whenever the legs were moved. At 6 weeks she started to snuffle and the snuffles gave rise to difficulty in feeding When seen at hospital at the age of 11 weeks the wrists and ankles were considerably enlarged and tender so that rickets was suggested as the diagnosis, although the patient's age was rather against this. The tibiae (legs) were markedly enlarged and appeared to be tender X rays disclosed generalized syphilitic epiphysitis and osteoperiostitis (Fig 63) and the W R. of mother and child clinched the diagnosis. Three weeks later the X-ray report was "Areas of osteitis filling in. Periosteal bone not so woolly

The child was treated for both syphilis and rickets, but she developed bowel trouble, from which she died at the age of 6 months.

(*c*) *Scurvy* Scurvy like rickets is prone to affect infants rather older than those usually attacked by congenital syphilis, but at times the signs

and symptoms may suggest a diagnosis of scurvy as in the following case

June S., born in June 1933 showed no signs of syphilis till she was 7–8 weeks old. She then developed a rash on the buttocks, snuffles and swelling of the left wrist. Other joints soon became involved and when the infant was seen at hospital with the complaint "that she was unable to use her limbs," the joints were so painful that the students suggested the diagnosis of scurvy (she was then 4 months old). Radiologically extensive syphilitic epiphysitis was seen (Fig 64) under treatment the osteitis diminished, while the supportive periostitis became more marked (at 5 months). Later the periostitis gradually subsided and it had practically disappeared when the child was 10 months old.

(*d*) *Infantile paralysis* On several occasions the clinical diagnosis of infantile paralysis made by a junior colleague or registrar has meant nothing more than the inability of an infant to move its arms or legs. This might have been due, amongst other conditions, to Erb s paralysis, infantile cerebral palsy (Little s disease) or Parrot s pseudo-paralysis. Acute poliomyelitis rarely attacks infants under 3 months of age. Polio-myelitis or polio-encephalitis may be encountered towards the end of the first year but, as is mentioned in Chapter 8 cases may be diagnosed as poliomyelitis or polio-encephalitis when they are really neurosyphilis.

(*e*) *Erythroblastosis foetalis* The difficulties inherent in the diagnosis between congenital syphilis and erythroblastosis foetalis and the co-existence of the two diseases in the same patient are referred to on p 242 As Caffey first emphasized (1937), some of the less-pronounced bone lesions of congenital syphilis may be seen by X ray in erythroblastosis, but severe lesions such as saw tooth metaphyses, foci of rarefaction at the angles between the junction of cartilage and shaft, and above all the characteristic cat bite lesion are not found in erythroblastosis or in any other variety of osseous pseudo-lues (to give it the name von Crefeld has suggested for these bone lesions) such as infantile cortical hyper ostosis (Caffey and Silverman)

Radiological findings

The lesions which may be seen in radiograms usually vary with the severity of the disease in the infant and particularly with any antenatal treatment the mother may have received during her pregnancy with this child.

1 A cap or plate of increased calcification at the end of the diaphysis of the long bones, which was formerly regarded by many observers as being the earliest evidence of syphilis in an infant is not diagnostic of the disease (Figs. 62, 63) McLean stated this in his monograph and we had made the same observation. Caffey (1937 1939) showed that similar appearances may be met with in other infantile diseases, such as erythroblastosis foetalis, staphylococcal and pneumococcal bacteriaemia, certain disorders of nutri

tion, and following the administration of bismuth to the mother during pregnancy



FIG. 63 Widespread osseous lesions in an infant aged 11 weeks the daughter of an untreated congenitally-syphilitic mother Clinical diagnosis of the enlarged wrists and ankles was ? rickets (snuffles at 6 weeks) Several fractures of the metaphyses are present (femur tibia, fibula) areas of rarefaction especially at upper end of tibiae and at the lower end of the left tibia. So-called epiphyseal separation No evidence of rickets seen

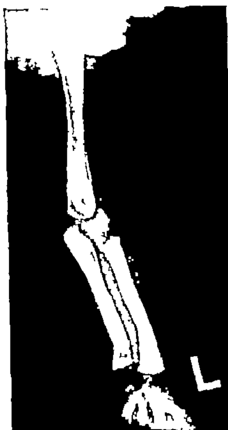


FIG. 64. Left upper limb of an infant aged 5 months showing well-marked periostitis of the lower half of both sides of the humerus and of the lower inner and upper outer sides of the ulna. There is definite angulation of the distal ends of the radius and ulna.

At 4 months the epiphyses were so painful and swollen that the diagnosis of scurvy was suggested by some of the students who saw the patient. Much more osteitis was then present and after only a week's treatment with mercury the improvement was considerable

2. The next stage in the process is a widening or deepening of the epiphyseal cartilage, which is the result of irregular or lawless overgrowth

and symptoms may suggest a diagnosis of scurvy as in the following case

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5. Periostitis and/or perichondritis may frequently be found associated with the osteochondritis, but this is only visible by X rays when calcification has occurred in the tissue laid down by the deeper layers of the periosteum (Figs. 62, 64). At times alternating layers of subperiosteal bone and marrow spaces may be seen, giving rise to the condition known as "periosteal layering" or "cloaking," and occasionally the whole shaft of the bone may be thus encased producing the "coffin" or "sarcophagus" type of lesion. It should be noted, however that periosteal cloaking is not diagnostic of syphilis, for it may occur in rapidly healing rickets with-



Fig. 66 Treponemata in a "rat-bite" lesion of the tibia from a child aged 9 weeks (× 1,850). Several parasites are present but it is unusual to find one in focus for so much of its length as is the treponema in the centre of the field. (Stained by Gordon's modification of Bertarelli and Volpino's method)

out syphilis being present (McLean). He states that in rickets the cloaking affects all the long bones and the whole of the bone-ends and shaft whereas in syphilis the distribution of the cloaking is less uniform and one half of the shaft is more heavily involved than the other. Periostitis is thus seen to be a late manifestation of Wegner's osteochondritis, and should it be found as the sole lesion present in early infancy it is probably correct to assume that the earlier stages of osteochondritis occurred during intra-uterine life. Fraenkel and Péhu state that ossifying periostitis unlike osteochondritis, does not respond to antispecific treatment but that it has usually disappeared by the end of the first year whether treatment has been given or not. We almost invariably found that this

infantile type of periostitis had disappeared by the age of 12 months, though admittedly practically all our patients who survived had received *constant treatment during the time.* The changes seen by X rays in the bones of syphilitic infants may show marked alterations in the contour of the bones and it is these changes in the contour of the bones, coupled with evidence of osteomyelitis and osteochondritis, which we regarded as being characteristic of congenital syphilis. We were not satisfied with the metaphysial cap and the submetaphysial rarefaction alone.

Site of the lesions

It is rather remarkable how considerable is the diversity of opinion as to the frequency and the sequence with which the various long bones are said to have been affected. In view of the large number of cases which are clinically negative and identifiable only on X ray examination, the earliest investigations of any value were those of Hochsinger which began about the year 1900 *He found the epiphyses of the elbow most affected.* Moro agreed with this finding, but he found also the femur to be a favourite site. In this he agreed with Schmidt Wegner Fraenkel and others. *Davidsohn found osteochondritis most commonly about the knee, as also* did Finkelstein Holt and Howland found the distal epiphyses of the femur and radius and the proximal epiphyses of the tibia and humerus most often affected. This corresponds in the main with our own experience, and one would unhesitatingly emphasize the frequency and importance of the cat bite lesion of the proximal and medial aspect of the tibiae for the diagnosis of congenital syphilis.

The two following cases are of interest in this connection the one because it affected an unusual bone the astragalus, and thereby misled both surgeon and radiologist the other because the pathological lesions were almost confined to one tibia.

Lucy A. born Dec. 1933 had no infantile manifestations of congenital syphilis but when about 5 months old developed a swollen ankle for which she was brought to the Children s Hospital. The joint was not very painful and it was thought to be either tuberculous or syphilitic. The Mantoux test was negative a Wassermann test positive. Dr Shires, our radiologist, diagnosed typical tuberculous osteitis of the astragalus with possibly some healing *periostitis* of the tibiae."[1] Because of his strongly-expressed view as to the tuberculous nature of the lesion, a W R. was repeated with a similar positive result. With antispecific treatment the W R. became negative at the end of 6 months and remained so for nearly 5 years. *Probably on the assumption that the lesion might have had a tubercular background the child was sent to Margate* to convalesce A few weeks afterwards she developed diphtheria and had to be

[1] This interesting radiogram was unfortunately lost when the basement of the hospital where the films were stored was flooded by a bomb falling on the hospital and fracturing a water-main No print or lantern slide had been made from the negative.

transferred to a fever hospital, where she contracted bronchitis and a spasmodic cough. She was febrile and lost weight. Shortly afterwards an abscess of the sternum discharged. There were physical signs in the chest, which was twice explored but without fluid being found. When about a year old she returned to Great Ormond Street, where an X ray showed the condition of the ankle to be "quiescent, with regeneration of bone taking place. The surgeon who had previously diagnosed tuberculous disease of the ankle now thought it was



Fig 67 Osteomyelitis and periostitis affecting mainly the right tibia in an infant 15 weeks old. The left tibia shows slight changes The first sign was a painless swelling below the right knee at 14 weeks. Fourteen days later slight changes were seen in the arms. At 9 months all radiological manifestations of the condition had disappeared

not a tuberculous condition. Apart from an attack of anaemia which followed a course of bismuth injections the child did well and walked without any difficulty or pain in the ankle until she was last seen at 4½ years of age.

Vera W born March 1932, had no early symptoms of congenital syphilis, but when she was 15 weeks old she developed considerable swelling below the right knee for which she attended the Children's Hospital, where she came under the care of Mr Twistington Higgins. By X ray characteristic syphilitic lesions were present in the upper part of the right tibia (see Fig 67) none of

the other limb bones appeared to be affected Treatment was started and within a fortnight the tibial condition had much improved, but slight changes were now present in the arm bones. At the age of 9 months the bones were healed and appeared normal. The brunt of the disease appeared to have fallen on a single bone—the right tibia (see also Harry G p. 200).

Possible relation of syphilitic osteochondritis to subsequent fractures

McLean and Harris pointed out that on careful examination with a lens alteration in the trabeculation of the bones could be recognized in good X ray photographs It has been known for some considerable time that in Albers-Schönberg's disease periodic variations in the intensity of the osseous sclerosis give rise to the formation of transverse bands of denser bone and that fractures of the bones are by no means uncommon. This is generally held to be due to decreased elasticity of the bone consequent upon its increased density and thickness. Several of our syphilitic children sustained fractures, and one not unnaturally thought that these fractures might have had some relation to changes in trabeculation and/or diminished elasticity of the bones the result of the infantile bone lesions 29 of our patients sustained fractures 3 broke two bones or limbs simultaneously and 4 of them broke bones on two different occasions. One boy broke his left arm and left leg at the age of $11^2/_{12}$ years and his left arm again a year later These facts and figures are of interest but the observations are too few to be of use in a statistical assessment of any possible association between osteochondritis and subsequent fractures

Dactylitis

Clinical dactylitis is not a common manifestation of congenital syphilis but routine radiological examination of the hands and feet reveals a considerable percentage of positive cases among infants under the age of 2 years Jeans and Cooke record 12 instances among 610 children under 2 years (2 per cent) They do not state, however if the cases were diagnosed clinically or radiologically Eleven of the 12 cases occurred under the age of 6 months and 1 at 14 months Two per cent was also the incidence Still recorded in his cases McLean encountered clinical dactylitis 6 times while investigating the bone changes in his 102 cases (6 per cent), but he gave no numerical record of the radiological cases in his series, since X ray lesions of dactylitis in the hands and feet are apt to be overlooked in routine examinations when the hands and feet are held closely opposed to the plate in order to ensure good results from the long bones of the limbs. On studying the records of 62 of his cases however it is found that X ray dactylitis was present in 17 or 27 4 per cent whereas clinically only 6 per cent had dactylitis. Of the 17 radiologically positive cases, 4 showed lesions of the metatarsal bones as well as of the metacarpal

bones and the long bones of the limbs their ages were 1 2 and 3 months (2). Of the 6 clinically positive cases 4 were under 1 year the other 2, 15 and 28 months respectively the last 2 were probably relapses of an early infantile lesion

In our own series of patients we had 9 cases of dactylitis 6 of them clinical and 3 detected radiologically The youngest of the clinical cases was 7 weeks the others were 10½ 11 and 16 months (Fig 68) $3^{4}/_{12}$ and $7^{10}/_{12}$ years respectively Two of these cases were unusual inasmuch as they showed no osseous lesions[1] (at 10½ months and $3^{4}/_{12}$ years) and the latter patient showed at the same time joint lesions which Still called pseudo-osteoarthritis (see Figs. 68 69) The case of dactylitis which occurred at $7^{10}/_{12}$ years was unique in our experience and the details may be of interest. The patient, a boy almost certainly suffered from epiphysitis in infancy for his mother gave a history of his legs having been stiff for about 14 days He first attended the Children's Hospital at the age of 11 months on account of snuffles and with a history of a sore mouth at 2 months. The W R. was found to be positive and the boy was given 4 courses of sulfarsenol and mercury iodide by mouth between the ages of 11 and 24 months. He then had 4 negative blood tests, after which he defaulted At $6^{4}/_{12}$ years he developed interstitial keratitis for which he attended a local hospital At $7^{10}/_{12}$ years his left hand became swollen and tender the right foot being also tender His doctor who was a former resident in our hospital, recognizing that the condition was an unusual one, himself brought the boy to the clinic. All the limbs were examined radiologically and the only bones to be affected were the left 4th and to a



FIG 68 Syphilitic dactylitis in an infant aged $1^{4}/_{12}$ years. By X ray slight osteoperiostitis of proximal phalanges of all the fingers present

[1] It is of interest that between the years 19 7 and 1938 the author saw more than 300 cases of gonococcal vulvo-vaginitis in his clinic and among them there occurred only one case of *clinical* dactylitis in a girl aged 7½ years *which by X-ray showed no bone changes* The details were as follows the ring finger of the right hand was affected also the knee and ankle joints. Later another finger and the second toe of the left foot were affected Gonococci were still visible in the vaginal discharge when the dactylitis occurred but Dr Orpwood Price f and the gonococcus complement fixation test persistently negative



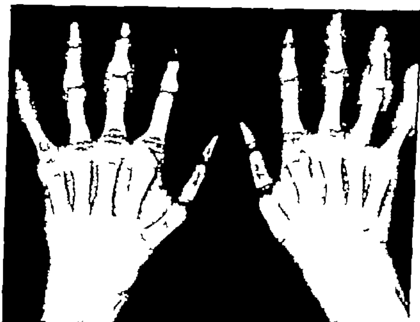


Fig. 69 Syphilitic dactylitis in a boy aged 3 4/12 years. The clinical photograph demonstrates the soft tissue swellings, but no bone or joint changes are discernible by X-rays. The patient's symptoms began with swelling of the knees and interstitial keratitis at the age of 2½ years. At 8 years of age the fingers were almost well and no bone or joint changes were seen by X rays. Still called the condition "pseudo-osteo-arthritis" (Sir Frederick Still's patient)

slight extent 5th metacarpal bones. The lesion was described by the radiologist as a periostitis, which is the osseous lesion frequently found associated with interstitial keratitis. The right foot, although it was tender showed no obvious lesion.

The 3 dactylitis cases detected radiologically occurred at 2, 3 and 8 months respectively The first of these cases was interesting chiefly because at 5 weeks typical syphilitic osteitis and periostitis of all the long bones of the limbs were present without any clinical signs of epiphysitis, and, after 3 weeks treatment with mercury and bismuth, the left knee and left elbow became acutely involved By X rays the osteitis was found to have progressed and the right big toe was found to be affected, although there was no clinical suggestion that this was the case. Thus was the only case of our series in which the bones of the foot were found to be affected, which bears out the observations of others that the toes are much less often affected than the fingers. Clinically the appearance of the affected fingers is characteristic and they are usually described as being flask or skittle-shaped. Formerly if the condition was not recognized and remained untreated, the swelling occasionally broke down and discharged through a perforation of the skin. Nowadays this must be a very rare occurrence, for we did not encounter a single instance during the whole of our experience.

The differential diagnosis between syphilitic and tuberculous dactylitis may have to be made. Both may occur in quite young infants, so that the age of onset or of the detection of the condition affords no clue to the diagnosis. The tuberculous variety may be tender and is much more likely to soften and break down than is the syphilitic form, which is as a rule, painless. A positive tuberculin test would be in favour of tubercle, whereas a positive W R. and concomitant signs and symptoms of congenital syphilis, including X rays of the limb bones, would strengthen the presumption of a syphilitic aetiology and the result of antispecific treatment would clinch the diagnosis.

The nature of the bone changes in congenital syphilis

There has been much speculation as to the nature of these bone changes. Wegner who originally described them under the name *osteochondritis syphilitica*, regarded them as being inflammatory in nature. In this he was followed by Herxheimer Hochsinger Fraenkel, Thomsen, Turnbull, Harris and others. Parrot, on the other hand, did not consider them to be inflammatory but of the nature of disordered nutrition or as he called it, a dystrophic lesion. Among those who agreed with Parrot were Barlow and several of his British contemporaries, Ekehorn, Schneider Pehu McLean and others. McLean mentions that as long ago as 1881 Pellizari and Tafani suggested a dual origin of the pathological processes (1) interference with the normal growth and development of bone, and

(2) specific inflammatory lesions—periosteal osteoperiosteal and gummatous Dennie and Pakula think that disordered metabolism of bone and cartilage plays the greater part in the aetiology of the lesions, and that inflammation plays only a minor part. In addition they make the suggestion that the process may be partly allergic. Caffey who has made a considerable study of infantile bones in syphilis and in other diseases of childhood, prefers the designation osteochondrosis to osteochondritis, since that name does not imply an inflammatory origin My own view is that the origin of the condition is certainly twofold or even more complex. The treponema is present, often in considerable numbers, especially at the growing ends of the bones—the epiphyseal cartilages—and under the periosteum (see Fig 66). By its toxic action it may (1) interfere with the orderly development and growth of bone and cartilage and give rise to the lawlessness of growth emphasized by McLean and (2) give rise to effects of a mildly inflammatory character which lead to the formation of fibrous tissue, to which Harris and Turnbull I think rightly give considerable prominence in their descriptions of the lesions. In addition to these two main causes, the treponema may act upon the haemopoietic tissues and thus give rise to an anaemia, in some cases so severe as to cause still further interference with the development of the growing bones

Congenital syphilis, rickets, craniotabes and Parrot s nodes

The relation between congenital syphilis and rickets and the part the two diseases respectively play in the causation of craniotabes and Parrot s nodes have long been a subject of controversy

Elsässer first described craniotabes in 1843 and concluded that it was essentially rachitic in origin. He gave this name to an abnormal thinness of parts of the parietal and occipital bones, so that with pressure of the finger tip the softened areas yielded like a piece of stiff parchment. Most European and American authorities agreed with this viewpoint until Wegner Parrot and Taylor successively demonstrated the bone lesions of infantile syphilis and so cast doubt upon the validity of the rachitic nature of craniotabes. Parrot regarded craniotabes as being due to congenital syphilis Various writers (Still, Graham, and Park and Eliot) have drawn attention to the fact that thinning of the skull does not always produce craniotabes as described by Elsässer A generalized softening may occur in premature infants and those with a mild degree of hydrocephalus. It seems likely that the cases of craniotabes described in congenital syphilitic infants without any other evidence of rickets have been instances of pseudo -craniotabes. True craniotabes occurring in children with congenital syphilis is almost certainly due to coexistent rickets.

Parrot s nodes are lens-shaped areas situated around the anterior fontanelle on the adjacent parts of the frontal and parietal bones The swollen area is intersected by a cruciform furrow, thus producing the hot

cross-bun head or natiform skull known also as the *caput quadratum* Occasionally similar swellings occur in the supra-orbital region of the frontal bone, and rarely a high forehead—the so-called Olympian brow—may ensue The nodes are probably due to periostitis and when the periosteum is stripped from the skull the underlying surface of the bone is seen to be covered by reddish, porous osteoid tissue Parrot believed these nodes to be syphilitic in origin and Carpenter Coutts and Findlay agreed with this view Barlow initially accepted Parrot's theory of their syphilitic origin but later in the light of subsequent experience, believed that they were rachitic. Still, Hochsinger and Park and Eliot have supported the idea that they are of rachitic origin.

Two factors contributed to the confusion in the earlier literature on the cranial lesions in congenital syphilis. Firstly that without X rays, serological or biochemical tests it may be very difficult to differentiate between congenital syphilis and rickets in an infant. Histological examination is of little help since the early bone changes in the two conditions are very similar Secondly many infants with congenital syphilis also had rickets. Some earlier writers claimed that syphilis was actually the cause of the rickets in these children to-day it would be more accurate to say that it predisposed to the condition. Other factors such as prematurity malnutrition poverty and neglect may also be mentioned.



Fig 70 Frontal bossing in a child aged $2^{11}/_{12}$ years. She suffered from mild hydrocephalus with square head, bossed forehead and prominent scalp veins when first seen at the age of 18 months. The child's C.S.F was positive for over a year and the father was being treated for tabes dorsalis. The patient's teeth are shown in fig 52

We did not see a large number of cases of active rickets or of patients in whom craniotabes could be elicited This we think is attributable to the increased care and attention given in this country to expectant mothers and to young children after the first world war and to generally improved social conditions We came to the conclusion that if Parrot's nodes were present during the first 6 months of life when rickets entered only slightly if at all, into the picture, congenital syphilis was almost certainly the cause In most of these cases there was some hydrocephalus and in some of them increased density of the skull bones. In patients 2 or 3 years old rickets, in the absence of syphilis, may give rise to a similar cranial deformity but the most

each of neo-arsphenamine and bismostab in the seventh to eighth month of pregnancy (Fig 72)

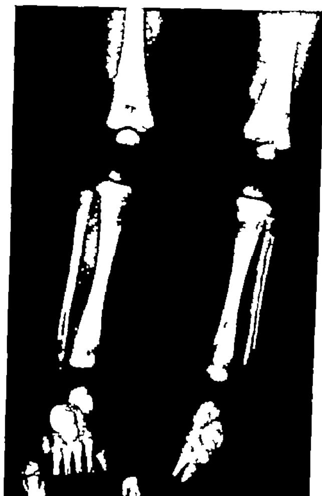


FIG 72 Unusually heavy lines near the ends of the long bones, probably due to mother's injections (N.A.B and Bi) during pregnancy from a patient aged 11 weeks Note the marked decalcified (rarefied) areas at the ends of the long bones and similar areas of rarefaction around the nucleus of the centres of ossification of the tarsal bones An early "cat-bite" lesion of the tibiae is also present The infant had no rash or snuffles and simply did not thrive Clinically epiphysitis of the wrists only was present X ray showed extensive bony changes

Another patient, Helen H., born in March 1937 was an illegitimate child of a congenitally syphilitic mother who was herself illegitimate The mother was

treated with arsenicals and bismuth during the last 7 weeks only of her pregnancy. There was a history of a rash in early infancy but not of snuffles or clinical epiphysitis. The child attended two hospitals before coming to us at

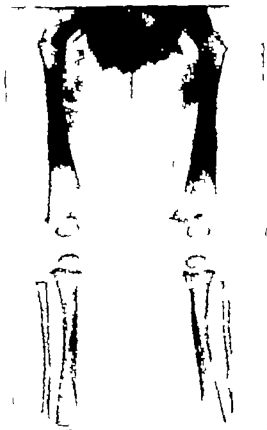


FIG. 73. Lower limbs of an infant 8½ months old. The bones show evidence of healed changes—particularly at the upper and inner aspect of the tibiae where the shape of the corticalis and the altered trabeculation indicate an earlier "cat-bite" lesion. Periostitis of all the long bones is present and several "growth" lines are visible. The centres of ossification, especially those at the lower end of the femora, have a definitely outlined periphery analogous to the growth lines in the diaphyses. The dark lines in the buttocks represent the successive injections of bisoxyl.

the age of 7 months. The W.R. was then strongly positive and X rays showed extensive osseous lesions in all the long bones, osteochondritis, osteitis and marked periostitis, the osteochondritis and osteitis being unusual findings in a

child of 7 months. The periostitis increased for several months and from the eighth month onwards "growth lines" were visible in the bones. At first two were seen in the radii a month later they were to be seen in the tibiae and femora as well as in the radii (see Fig 73). At 15 months the growth lines were increasing in number and some sclerosis of the cortex of several bones, especially the tibiae and femora, was present. A month later 5 growth lines were seen in each of the bones, the oldest line having disappeared. At 18 months the osseous lesions were almost healed, the growth lines were still visible and the radiologist commented upon undue prominence of bony trabeculae. During the 12 months that 10 serial X ray photographs were taken the patient was receiving weekly injections of bisoxyl in courses of 12, with 4 weeks interval between the courses. Unfortunately no lantern slides were made of these radiograms at the time and the negatives were destroyed by enemy action in September 1940, so that no permanent record is available of this interesting case.

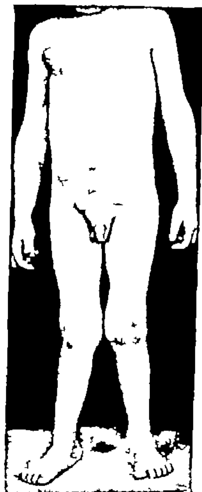


FIG 74 Photograph at the age of $4^{11}/_{12}$ years showing the enlarged knees (Clutton's joints) and a moderate degree of knock knee

The following case report of Arthur W is interesting from several points of view but also puzzling, and as his bones showed growth lines at one period of his development his record is given here. He was born in Oct. 1930, but did not come under our observation until he was 4½ years old He is said to have had a rash on the face when 3 months old, but there is no history of snuffles or epiphysitis. At the age of 3¾ years his eyes became inflamed and from the history it would appear that he suffered from interstitial keratitis, though the hospital he attended wrote upon inquiry that he was treated for phlyctenular conjunctivitis. Six months later the knees began to swell but did not become painful. At a children's hospital the diagnosis of Clutton's joints was made and he was sent to us at Great Ormond Street for treatment. Several radiograms were taken of the lower limbs from the age of 4½ years onwards. At first no changes were discoverable in the bones or epiphyses, but only the increase in joint fluid and periarticular tissues characteristic of Clutton joints. At the age of $4^{7}/_{12}$ years our radiologist (Dr Shires) reported Swelling in the joints Slight rarefaction in the epiphyses. Periostitis of shafts of femora and doubtful of tibiae." The last radiogram taken at 5¼ years showed "definite irregularity of epiphyses, suggesting a chronic arthritis, also spacing of the joints.

Many horizontal lines of calcification also great thickening of the compact bone of femur (chronic osteitis) (see Figs. 74, 75). The radiologist gave it as his opinion that the lines of calcification suggested an illness since the previous radiogram was taken about 14 months previously when the lines were not present. The only "illness" recorded was a blow on the eye which became inflamed again and nebulous 2 months later when the eye had improved, the patient developed herpes of the lip and 3 months later still, at $5^{4}/_{12}$ years, the herpes recurred and with it the right eye flared up. During all this time the boy was receiving weekly injections of bismuth and *mist. pot. iod.* by mouth, and it is impossible to say with certainty whether the administration of bismuth



Fig. 75 Same patient as shown in Fig 74. X-ray at 5½ years showing several growth lines suggestion of chronic arthritis and osteitis and spacing of the joints" (Dr Bhites) as mentioned in the text

or the recurrent eye trouble and the attacks of herpes were the cause of the lines of calcification and the thickening of the compact bone of the femur

The joint and bone lesions were not the only puzzling features presented by this patient, for it was by no means certain that he had congenital, as opposed to acquired, syphilis (see p. 446). It is true that there was a history of a rash at 3 months and that when seen he had a big bossed head and rhagades at the angles of the mouth and lips, but the blood W R.s of his parents and three sibs were all negative, whereas the patient's W R was positive for 4 years. He was traced after 3 years residence in the provinces, when it was reported that he looked healthy the teeth were poorly developed but not Hutchinsonian or Moon and there had been no relapse of the interstitial keratitis or of the arthritis (1939).

The Bones in late Congenital Syphilis

Pathology

The pathology of the osseous lesions of late congenital syphilis is fundamentally similar to that of the lesions of infantile bones—namely the well known reaction of the tissues to the treponema in the form of a perivascular cellular granulation tissue In the infant the treponema is

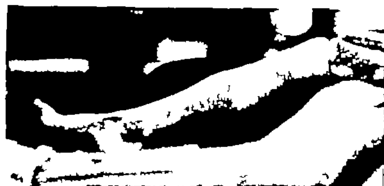


Fig 76 Gumma of tibia showing an area of softening at the centre in a boy aged 11 years

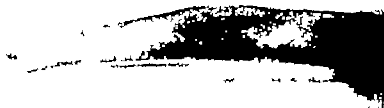


Fig 77 X ray showing the rarefied area (softening) near the middle of the gumma Note the thickening of the cortex of the bone (osteo-sclerosis) The fibula also shows some thickening (Sir Thomas Fairbank s patient treated in the author s clinic)

found most often in the growing cartilage whereas later on in childhood the favourite haunt of the parasite is the deeper vascular layer of the periosteum The lymphangitis (of Allbutt) spreads from the periosteum to the Haversian canals of the bone, and it has been suggested that the tension produced by the granulation tissue within the bony canals is responsible for the nocturnal boring pains so often associated with osseous syphilis (Boyd).

1 The essential lesion is a *hyperplastic osteoperiostitis* which may be

diffuse, frequently leading to sclerosis of the bone, or localized—the periosteal node or gumma—which leads to necrosis and softening. Both changes may occur in the same bone or in different bones in the same individual. The tibia is most commonly affected, but other limb bones and the flat bones—skull, face, nose, palate and sternum—may also be





FIG. 78. Massive periostitis of left tibia in a boy aged 7½ years. History of a fall on the leg 5 months previously. The left ulna was also affected.

FIG. 79. Same patient as Fig. 78. The X-ray appearances were much more marked than they had been 7 weeks earlier despite the fact that some treatment had been given. (Sir Lancelot Barrington-Ward's patient.)

affected. The periosteal node or gumma is a localized firm swelling, frequently tender or painful, situated usually on the anterior surface of the tibia. Although localized the lesion is not sharply defined but gradually shades off on to the surrounding bone (see Figs. 76 and 77). Sometimes the whole length of the tibia may be implicated (as is seen in Figs. 78 and 79). In addition to the periosteal hyperostosis there may occur a

hyperplastic endochondral ossification at the epiphyseal junction which leads to overgrowth of the leg and so giving rise to a form of gigantism. In osteoperiostitis the underlying bone becomes at first somewhat rarefied but soon afterwards the characteristic sclerosis of syphilis sets in, osteoblasts converting the connective tissue into bone. Later still probably owing to a reduction in the blood supply consequent upon syphilitic endarteritis, a gumma may soften and break down in the characteristic fashion, ulcerate through the skin and expose bare bone (Figs 76, 77).

2. In *diffuse osteitis* which is a rarer form of syphilitic bone disease, the greater part or the whole of a bone may be involved from one articular cartilage to the other and from periosteum to medulla. The pathological process is essentially the same as before, but now the changes are more extensive—new bone laid down (*a*) under the periosteum, giving rise to a marked thickening of the shaft (*b*) on the walls of the Haversian canals, resulting in increased density of the bone and (*c*) in the medulla, possibly leading to actual obliteration of that cavity The entire bone is now dense and heavy Gummatous osteitis, analogous to the periosteal variety may develop the gumma being deep-seated and often extending across the whole width of the bone. Occasionally this may result in a pathological fracture. If such a gumma ulcerates to the surface it may become secondarily infected and pyogenic osteomyelitis ensue. Rarely the destructive process may invade a nearby joint with resulting ankylosis. We did not meet with such a case, but Jeans and Cooke record 2 cases, one in an elbow the other in a shoulder

Clinical features

Osseous syphilis in older children may start suddenly with a feverish attack or with pains in the limb in a certain proportion of cases a history of trauma can be elicited It seems likely that the treponemata have remained dormant after an infantile infection of the bone and may later be reactivated by an injury We obtained a history of trauma in 10 of our 47 cases. Sometimes tender pinkish nodules may be seen along the anterior border of the shin which closely resemble the lesions of erythema nodosum and have been diagnosed as such. The pains in the limb which sometimes usher in the disease, and are usually stated to be worse at night, may give rise to the diagnosis of growing pains or of rheumatism. In our experience severe pain was not a common symptom of osseous syphilis, for in only 2 of our 49 patients who suffered from periostitis or osteitis was the pain so great that the patients screamed at night because of its severity In one or two other cases pain was complained of but it was not intense. A little later with the progression of the osseous lesions, walking may be interfered with, and by the time the patient is brought to hospital the limb may be very definitely enlarged (Fig 79) and hot to the touch. The edge of the tibia is rounded off and obvious nodules may be

felt along its course. In younger patients the pathological lesions may be limited to the periosteum and if treated early the condition may resolve entirely. It is in older children and the more chronic cases that the bone becomes thickened and sclerosed, especially anteriorly. The tibia then shows a bowing forward which is known as the "sabre" or "cutlass" tibia (see Fig. 80). A somewhat similar deformity of the tibia may result from rickets, the difference being that whereas in syphilis the bowing occurs



FIG. 80. X-ray of a syphilitic tibia showing forward bowing (sabre tibia) in a patient aged 10 years. Three years previously the tibia was hypertrophied in its whole length, with two areas of softening. The inguinal glands were enlarged and the clinical diagnosis lay between chronic osteoperiostitis, syphilis and sarcoma of tibia (see pp. 225 and 227)

about the middle of the bone and is due to osseous thickening, in rickets the curvature occurs about two-thirds of the way down the length of the bone, which is less opaque to X rays and does not show any thickening.

Distribution of the lesions

Table 10 shows the distribution of the condition among the various bones in our 49 cases, from which it is seen that the tibia was affected in no fewer than 41 patients. In a few cases we found that a neighbouring

joint became swollen, usually subsequent to the inflammation in the bone itself. In one patient an attack of interstitial keratitis some time antecedent to 4 years of age, was followed by redness, swelling and pain over the right shin-bone, pain in the left arm and swelling of the elbow and subsequently by swelling of the right knee. The mother's own statement was that the child had suffered from "rheumatism" for 6 months. Despite the history of eye trouble some time previously the clinical diagnosis was "rheumatism," though the notes stated that no nodules were present and there was no limitation of movement. The right tibia was inclined to be "sabre shaped." A subsequent blood test gave a positive W.R. and the child was treated with mercury and potassium iodide. After 6 months outpatient treatment on these lines, the patient was brought to the hospital very ill and as a medical emergency she was admitted to a different ward. Here she had the advantage of treatment with arsphenamines, to which she rapidly responded. She was followed up until she was 19 years old when her joints, eyes and ears were all functioning well but the patient seemed anaemic. Her blood W.R. and *cerebrospinal fluid had been negative for nearly 10 years.*

TABLE 10

The Distribution of the Lesions in 49 Patients with Late Osseous Syphilis

1 tibia	14	Both tibiae	13
1 tibia, 1 fibula	3	Both tibiae, gumma fibula	
1 tibia, femur	1	Both tibiae, arthritis knee	
1 tibia, 1 ulna	2	Both tibiae, left radius	1
1 tibia, 1 elbow, later knee swollen	1	Both femora and ? also tibiae after Clutton	1
1 tibia with ? Clutton knees			
Arthritis of knee with palate	1		
Arthritis of knee (old osteitis)			4
1 tibia in 24 patients		*1 or both tibiae attacked in 41 patients*	

In 8 of the patients in whom the tibiae were unaffected the bones affected were as follows: (1) both femora (at 2 years), diagnosed as "? T.B. hips," (2) one femur, (3) femur and arm, (4) one fibula, (5) one elbow, (6) one "elbow," ? fractured olecranon, (7) one hand (metacarpal bones) and foot, and (8) one case with skull and lumbar vertebrae.

Another patient whose bone and joint lesions led to an early suggestion of rheumatism and later proved to be *syphilitic had the following history.*

He was a boy aged 9 (12) years, with one week's history of pain in his shin bones which made him scream at night. When seen at the Surgical Outpatients Clinic he looked pale and ill; both tibiae were swollen and tender and the tentative diagnosis was "? rheumatic periostitis." An X-ray report stated "increased density centre of right tibial shaft, suggesting a localized osteoperiostitis." A W.R. of the blood gave a strong positive and the treatment given comprised mercury with chalk and by inunction, and potassium iodide. Within a month the lad developed effusion into both knee joints. Treatment was very irregular as the boy lived several miles from the hospital and there were several younger children *in the family.* In consequence progress was slow and at the end of 3 years the right knee was still slightly swollen. He was last seen at the age of 14

years, when his blood and spinal fluid were found to be quite normal. We were unable to get the patient to attend hospital again, but when he was 17½ years old, the mother wrote saying "The lad was very poorly after the lumbar puncture. He now looks in perfect health and he has won 2 cups. He ran 3 miles in 16½ minutes." He had evidently completely recovered from his periostitis of tibiae and Clutton's knees of 8 years before.

One of our cases showed a rarefied area in the head of the fibula which was thought to be a gumma in this situation. Another case affecting the fibula occurred in a girl 11 years of age in whom there was disease of the upper third of the right fibula and also an abscess in the right foot. Probably on the assumption that this was due to osteomyelitis or tubercle, the upper third of the bone was removed no tubercle bacilli or other organisms were found in it, but a W R. done subsequently was positive and the child was given the appropriate treatment Hochsinger states that the fibula is also affected in most cases with the tibia, but our experience with 41 patients with affected tibiae and only 3 cases of affection of the fibula does not lend support to his view

The association of the bone and joint lesions of late congenital syphilis with interstitial keratitis will be considered in Chapter 8 (p 335)

Diagnosis

As has already been stated, the condition may be regarded as being of rheumatic origin on account of the pain and of swelling which may occur in adjacent joints. Radiologically although the diagnosis can easily be made in the later stages owing to the density of the bone, in the early stages of periostitis before calcification of the new granulation tissue has occurred, the X ray may only show an indistinct outline to the bone.

Tubercle undoubtedly may have to be diagnosed from these lesions, and in this connection the main points to be borne in mind are that syphilis affects the diaphysis of the bone rather than the articular ends secondly the new bone formation in syphilis is sclerotic in type rather than rarefied as in tubercle and thirdly in syphilis the joint is seldom involved, whereas in tubercle this is commonly the case.

Syphilitic lesions may also have to be differentiated from malignant disease of the bone such as sarcoma of the tibia, of which we had one instance only (Fig 80), or metastases of a Wilms tumour or of a neuroblastoma, which might be mistaken for gummata or syphilitic osteoperiostitis These mistakes can be minimized or avoided by *doing a Wassermann test on every patient with disease of bones or joints*

Osteoperiostitis of the skull

Jeans and Cooke mention 3 patients with disease of the skull bones, aged from 11 to 13 years, all of whom had multiple bone syphilis and with

lesions also of the frontal or occipital bones, with ulceration of the superficial parts. Ethel Dunham also reported 2 cases in girls 8 years of age, and all of these cases apparently suffered gross neglect. We have not encountered such bad cases ourselves, only one in our series having had disease of the skull bones. This patient, of whom the early history was very incomplete, was sent to us by the London County Council authorities at the age of 13 years on account of interstitial keratitis of 3 months duration The history was that at the age of 9 years she suffered from syphilitic periostitis of the frontal bone, for which only a few injections of Kharsul phan were given. Three years later at the age of 12 she had trouble with the spine and on X ray examination it was found that the third lumbar vertebra was affected the radiologist stating that it was definitely not tuberculous and he considered it to be syphilitic.

Reference has already been made (see p. 138) to the fact that in congenital syphilis, especially in cases which had been neglected or were latent, syphilitic disease of the bones of the palate and nose may occur often leading to considerable destruction and loss of tissue. In such cases perforation of the palate may persist and or there may be very considerable scarring and deformity of the soft palate, with absence of the uvula. The condition known as saddle-nose is also the result of disease of the nasal bones and nasal septum.

Syphilitic disease of the spine

We have notes of only one case—referred to above—of syphilis affecting the spine Woringer (1929) wrote a paper on Syphilitic Pott s Disease in which he reported a case aged 11 with gummatous osteitis of the fifth lumbar vertebra. The condition had existed for more than 2 years and had produced sensory and motor nerve disturbances It responded well to antisyphilitic treatment Hochsinger says that the condition is very rare in infancy and that he had had 7 cases of syphilitic cervical spondylitis between the ages of 3 and 7 years

Cases showing post infantile bone lesions

Gladys R. born Dec. 1914, showed no infantile or other symptoms until she had osteoperiostitis of both tibiae at the age of $8\frac{10}{12}$ years. For 2 years the child received no antispecific treatment until she was brought to Great Ormond Street, when it was found that her teeth showed typical Hutchinson and Moon characteristics. She was getting deaf and the suspicion of syphilis was confirmed by a positive W R. in the blood. Some of the teeth were extracted and Mr Pitts, our dental colleague, thought the patient may have had a gumma of the upper jaw as there was a good deal of bleeding and destruction of tissue when the teeth were extracted. The child was treated over a period of 3 years with bismuth and neo-arsphenamine, during which time she had 6 rather severe attacks of interstitial keratitis.

Amy R. born Nov 1914. No early history available, but at 7 years of age the patient was admitted to the ward with two large fluctuating masses, the size of walnuts, on the left tibia. The first diagnosis was ? sarcoma of the tibia. Radiological examination showed, however that there was bony overgrowth with abscess formation and in places sclerosis of the bone. The facies was suggestive of syphilis and the blood test confirmed this suspicion, from which it was concluded that the tibial lesion was a gummatous and sclerosing periostitis. After 3 years treatment the condition healed and by X ray there was forward bowing of the tibia, but all signs of osteitis had disappeared. (This case was referred to on pp 223 and 225)

The Joints in Congenital Syphilis

Infantile

The joints may occasionally become involved in early congenital syphilis. Barlow (7) (1880) and Heubner (1881) stated that true suppurative arthritis occasionally occurred in connection with the affected epiphyses of syphilitic infants. The lesion was due to secondary infection and independent of the syphilitic process. Four of our patients, all at or under the age of 3 months, suffered from suppurative arthritis. In the first case pus was discovered in the child's right elbow joint post mortem at the age of 2 months the causal organism was the pneumococcus. The left elbow contained turbid fluid but no organisms could be seen in it. In the second patient, aged between 2 and 3 months, the pneumococcus was isolated from an elbow and the patient made a good recovery with full use of the joint. Case 3 also an elbow case, was interesting inasmuch as at the age of 2 months there was no sign of epiphysitis, either clinical or radiological. At 3 months there was still no clinical epiphysitis, but radiologically there were signs of osseous syphilis. Two weeks later pus was obtained from the elbow joint, from which *Staph aureus* was grown. The child recovered. The fourth case occurred in a child aged 3 months. The shoulder was affected in this patient and streptococci were isolated from it. The arthritis cleared up with the help of an autogenous vaccine and there was no impairment of the joint. The boy developed into a healthy lad with a negative W R. to the age of 18 years, when he unfortunately sustained a fatal motor-cycle injury

Late (syphilis congenita tarda)

In late congenital syphilis joint lesions are more frequently met with than in the early form. The commonest type is the bilateral, more or less painless, effusion into the knee joints first described as a clinical syndrome by Clutton in 1886 Dunlop who collected 16 cases from the records of the Edinburgh Sick Children's Hospital (1904) states that von Hippel found joint involvement in 56 per cent of his cases of congenital syphilis, that Hutchinson had 20 cases and Clutton 11 Still records

7 joint cases among his 100 patients, 4 of the osteoarthritic and 3 of the Clutton type. Fournier recorded synovitis in 82 of his 212 cases (38·7 per cent) of syphilis congenita tarda. It is noteworthy how frequently in these cases the knees are attacked in von Hippel's 43 cases the knee was involved in 41 and in 5 cases it was the only joint attacked. In Clutton's 11 cases both knees were attacked *in every case all the patients* but one had past or present bilateral interstitial keratitis, and 4 of them had osteitis of the tibia. In one patient, aged 20 years, there was an interval of 2 years between the involvement of the first and second knee, and in only one patient was any other joint affected when both ankles were swollen at the onset of the arthritic syndrome. It may be noted that although Clutton himself mentioned that in one of his patients the knees were very painful at the start, and that in two others there was very definite tenderness about the joints, subsequent writers when referring to Clutton's joints almost invariably describe them as being *painless and bilateral*, thereby suggesting that a *painful* affection of a *single* knee joint must be *tuberculous or rheumatic in origin, and that congenital* syphilis need not be considered in the diagnosis of the condition. We had several cases in our series where a bone or joint lesion had been erroneously attributed to tuberculosis or rheumatism, when the blood and therapeutic tests showed that congenital syphilis was really the cause

Among our 465 congenital syphilis patients over 2 years, 338 had lesions of active syphilis, which included 61 joint cases or 18 per cent. These *joint cases fell in the following groups*

TABLE II

Joint Lesions in 465 Congenital Syphilis Patients over the age of 2 years

Group 1	Typical Clutton's joints	40 patients
Group 2.	Synovitis or arthritis of knee following trauma	8
Group 3	Synovitis of knee associated with periostitis in adjacent bones	4
Group 4.	Arthritis of obscure or unknown aetiology affecting other joints in congenital syphilitic children	8
Group 5.	Osteoarthritic type	1 patient
		61 patients

In addition we had 2 interesting and obscure arthritic cases in seronegative *children whose mothers were undoubtedly syphilitic.*

Clutton's joints may occur at any age up to 21 years, possibly even beyond. Our patients varied from 3½ to 18 years, the commonest age of onset being between 5 and 10 years. The sexes were about equally affected. In many cases the condition seemed to start without any warning but it is probable that a slight trauma or a mild periostitis of an adjacent bone may be the prelude to an attack of synovitis. In 8 of our cases there was a definite history of injury and such cases are usually diagnosed as *traumatic arthritis* particularly if there should be pain in the joint and its temperature raised. In the majority of our cases both knees were

affected, but in 3 of them only one knee was involved (right knee once, the left knee twice) All 3 of these single joints were diagnosed as tubercle In 2 other cases in which both knees were affected and the temperature was raised, the condition had been diagnosed as rheumatic fever

A patient with Clutton's joints presents a rather striking appearance

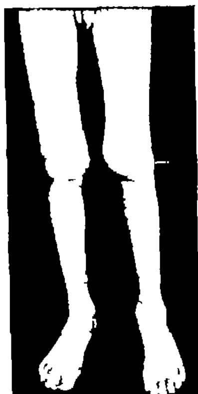


FIG. 81 Clutton's joints in a boy aged 9 years. Both knees were painful at first and then became swollen the pain soon passed off The boy was kept at rest for several weeks and when seen at the Children's Hospital to which he was carried the thigh and leg muscles were very wasted After one injection each of neo-arsphenamine ("914") and bisoxyl he was able to walk in a few days, and after six months antisyphilitic treatment the knees were normal

with the baggy enlargement of both knees (Figs. 76, 81), and the enlargement may be accentuated by the wasting of the thigh muscles which supervenes if the patient has been kept in bed or on a couch for a considerable time. More than half our Clutton patients complained of pain in the joints to a greater or less extent, and in a few the joints were distinctly tender and hot to the touch. On X ray examination no osseous

of Disease in Childhood in May 1903 It occurred in a boy aged 10½ who had interstitial keratitis in the left eye a few months previously Soon after the eye was attacked, the finger joints of both hands became swollen and when the patient was shown to the meeting the first interphalangeal joints of all the fingers were enlarged as were also the metacarpo-phalangeal joints of the right hand. It was noted that the swelling was periarticular rather than due to bony enlargement and that the condition resembled that seen in osteoarthritis. Dr George Carpenter and Dr Parkes Weber both thought the condition was due to congenital syphilis and not to osteoarthritis. The latter called it the "phalangitis of congenital syphilis," otherwise known as syphilitic dactylitis, and mentioned that it had been studied by Hochsinger who had pointed out that one of the diagnostic signs of the disease, when the metacarpal bones as well as the phalanges were affected, was that the swelling was chiefly at the distal ends of the metacarpal bones, that is to say in the neighbourhood of the epiphyses. This diagnostic feature was strongly marked in the case shown to the meeting

Still, as has been mentioned recorded 4 cases of this type among his 100 cases of congenital syphilis (1908) We, on the other hand, among 900 cases of the disease, saw only one patient with arthritis of the rheumatoid or osteoarthritic type which by a coincidence was originally a patient of Dr Still's at Great Ormond Street in 1923 The child's W R was strongly positive, but it responded readily to treatment and became negative in about 2 years with mercury treatment alone. Still called the case one of "pseudo-osteoarthritis" and the condition is well shown in Fig 69. The radiograph of the knees showed some periarticular thickening and that of the hands thickening around the interphalangeal joints, in each case without any osseous changes The condition started originally at the age of 2½ years, when both knees became involved and bilateral interstitial keratitis appeared at the same time. A later photograph, taken at the age of 8 years, showed the fingers almost normal)

The last two cases to be reported in some detail are of considerable interest, inasmuch as they both occurred in children whose mothers were undoubtedly syphilitic, the children themselves being possibly syphilitic but with negative serology (C cases). Both patients exhibited unusual clinical features and in several respects the second case resembled the chronic osteo-polyarthritis of congenital syphilitics described by Nobécourt and other French writers

Cases in W.R. negative children of syphilitic mothers

P M., born 1928, had no infantile symptoms of syphilis but a hydrocele at 3 months. This was operated upon and very shortly afterwards the ankle became affected, so that the child had not walked when he first attended hospital as a patient under Sir Lancelot Barrington Ward at the age of 2½ years. He

then had a swelling of the right external malleolus, but on radiological examination no changes could be seen in the bones. Shortly afterwards the internal malleolus became painful and clinically there was obvious swelling of both malleoli. There was nothing abnormal in the joint. The condition was thought to be possibly tuberculous and a back splint was applied. Two weeks later the bones were still expanded and warm to the touch and despite the negative X ray picture, osteitis of the lower end of the fibula was thought to be present. A further radiogram was taken 3 months later when again nothing abnormal could be detected in the bones, but the ankle was still swollen and hot and the mother said the child had more pain in it. A W R. of the child's blood was quite negative, and on inquiring into the mother's history on this occasion, we ascertained that the husband was an old soldier and that the mother had had a stillbirth and a miscarriage before the patient. Her blood was thereupon tested and found to give a positive W R. The child was given mercury treatment and later "Orarsan" with a certain amount of benefit. Later in the year a Mantoux was done which was strongly positive. We were now faced with the alternative causes, tuberculosis or latent syphilis, or indeed a possible combination of the two. At the age of 4 the patient suffered from haematemesis and melaena and his condition was unsatisfactory for several months afterwards. At the age of $5^{1}/_{12}$ years the right leg was very wasted, having been in a splint for some time, and the surgeon expressed his opinion that "this was certainly not a clinical case of tuberculous ankle. An X ray report said "Erosion of adjacent articular surfaces of the ankle joint—swelling of joint subsiding." An X ray taken a year later showed that there was "further erosion of the epiphyses and astragalus, and at $7^{2}/_{12}$ years the radiologist reported that "further destructive changes had occurred in the right ankle." The child then went to a convalescent hospital, where he improved very much in health, and although the ankle was still tender he could walk on it at the age of 9. This case is undoubtedly one of considerable interest because it raises the question whether a tuberculous lesion grafted upon syphilitic soil such as the child of a syphilitic mother might possess, may run an abnormal clinical course and be so atypical as this case proved to be. In many respects this case resembles that of Lucy A. (see p 206). It also illustrates the importance of taking a careful family history in all cases. Failure to do so in this case led to a delay of nearly 5 months in examining the patient's and his mother's blood and the finding of a positive W R. in the mother while the child's W.R was negative stresses the importance of examining the mother's as well as the child's blood in every case in which syphilis is suspected.

One of the most interesting of our joint cases was that of P.Z. who was born in 1921 He had no infantile symptoms of syphilis and was quite well until he reached the age of 11 months. He then had an attack of dysentery with blood and mucus in the stools. The mother is said to have contracted the infection through nursing the patient. The child's dysenteric attack was followed almost immediately by trouble in the joints, first the knees, then the ankles and wrists. There was no recurrence of the bowel trouble, but the joint affection persisted. The painless effusions into the joints led the medical officer of the local hospital to suspect syphilis and blood tests were taken from mother and child. The mother was found to be positive and the child negative The latter was given treatment—not antisyphilitic—for the joint condition for a further 18 months, but there was no improvement. In view of his mother's positive W R. he was then given antisyphilitic treatment (details unknown) which was apparently followed by a temporary improvement in the condition of the joints, which,

however was not maintained. At the age of 6½ years he was admitted to the Children's Hospital Great Ormond Street, under the care of Sir Robert Hutchison, when his condition was carefully investigated. Agglutination tests were carried out on the blood of both mother and child with various dysentery organisms, but with inconclusive results. A Wassermann test on mother and child confirmed the result obtained at the local hospital namely that the mother was positive and the child negative. The child's blood was re-examined on several occasions, once after provocation, but each time with a negative result. The joints were examined radiologically in June and Oct. 1928 and on neither occasion could definite bone changes be seen. On the second occasion, however some creaking was felt in the joints, especially the right. In March 1930 both knees were much more swollen again no bony changes were seen by X-ray and 20 ml. of slightly-turbid fluid was aspirated from the right knee, and the following week 20 ml. of fluid from the left knee no organisms could be found on either occasion. The W R. of the fluid was negative. The arms were also examined radiologically and again no bone changes could be found there was no indication as to the nature of the arthritis. The knees and wrists continued to enlarge and the patient was admitted several times for investigation and treatment. In 1933 the antra were found to be opaque, but the washings were clear The effusions into the joints materially diminished under the influence of counter-irritation with iodine.

The patient was seen again when nearly 16 years old, when he was able to get about quite well in spite of considerable swelling of the knees. A photograph and radiogram were taken, the latter showing rarefaction of bone The elbows were also enlarged and the limbs could not be fully extended. W R. and Kahn were negative The patient was finally seen at the age of 23, when his condition had deteriorated and resembled a subacute rheumatoid arthritis, many of the smaller and medium-sized joints of the upper and lower limbs being affected

The family history was interesting The mother's first husband acquired syphilis in 1915 during the first world war and was treated in the Army He died of wounds in France. They had 3 children, born in 1912, 1914 and February 1916 respectively who all appeared to be healthy The mother remarried and had 3 boys by her second husband. None of them exhibited symptoms of infantile congenital syphilis and all 3 had negative serological reactions, although the mother's W R. was strongly positive on three occasions—the last being when the youngest boy was 4 years old. The eldest of the 3 boys was Percy whose history has just been related. The second boy was mentally defective, which was attributed to a fall on the head and the youngest at 7 years had septic tonsils and cervical adenitis but was otherwise well

The patient obviously suffered from a subacute or chronic "rheumatoid or osteoarthritic affection but it is impossible to say if this was due to a dysenteric toxin, a syphilitic soil or a more ordinary cause, or to two or even all three causes combined.

Diagnosis and treatment

In the diagnosis of joint lesions it is most important to bear in mind the possibility of syphilis, even when a history of a trauma has been obtained. It is natural after an accident to ascribe the joint lesion to the trauma and to call it a traumatic arthritis and to treat accordingly but it is important to remember that a trauma in many cases may arouse dormant treponemata into activity so that what may appear to be a simple traumatic

arthritis is in reality a syphilitic arthritis occasioned by the combined effect of the trauma and the treponema. In our joint cases there was a history of trauma in at least 8 so in the interests of the patient it is desirable that a blood test should be carried out in every case of a subacute bone or joint lesion, even if a trauma seems to be a sufficient cause of the condition. One should also inquire into the history of interstitial keratitis and examine the patient for the presence of stigmata of congenital syphilis. In the absence of trauma an enlarged joint may suggest rheumatism or tuberculosis, and amongst the cases reported above 6 were called rheumatism and 4 were thought to be surgical tuberculosis. One may add that although there is no known reason why a Charcot's joint should not be met with in congenital syphilis, we did not meet with such a case in our series, and very few authentic cases of Charcot's joint have been reported in the literature.

Sir Thomas Fairbank, in an experience extending over many years, was able to refer in his "Atlas" to only one case in the literature, that of Dudley Buxton in a girl aged 17 years (1925) in which the hip joint was affected. Bingold (1952) reported a case in a girl aged 15 years who suffered from polyostotic fibrous dysplasia with pathological fracture of the left hip. It was then discovered that she was also suffering from juvenile tabes, and within a year after an operation on the hip there was complete disorganization of the left subtaloid joint which necessitated an amputation below the knee. The blood and spinal fluid had both given positive serological tests, but that of the cerebrospinal fluid was reversed to negative by the antisyphilitic treatment given. The parents and 7 other sibs all gave negative serological reactions and no history of syphilis, so it must be concluded that although the tabes was juvenile it was not congenital and that the patient's syphilis was acquired, probably in early infancy in one of the ways outlined in Chapter 13.

Therapeutically the routine treatment with arsenicals, bismuth and mercury was what we employed in our series of cases, and the majority of them responded rapidly to this line of treatment. One case cleared up fairly quickly on oral stovarsol. Only very occasionally did we find it necessary to put the limb into splints, because it is better for the patient to be up and about, provided this does not give rise to much pain and the limb is not wasted through delay in treatment. In an isolated case it might be desirable to keep the patient in bed for the first week or two of the treatment, applying massage to the muscles, but the sooner the patient can be up and about the better. In older children it was customary to give potassium iodide in addition to the other treatment, because this was found to reduce the pain which was frequently present at night. We usually had good results from treatment with the arsenicals and mercury or bismuth compounds, but we have notes of at least two cases in which there was an increase in the periostitis for some weeks after treatment was begun, and in one of these cases the left leg became considerably larger and hotter than the right even after *such* treatment had been given.

To-day the treatment would consist of penicillin in the usual dosage

used either alone as is general in the U.S.A or together with arsenic and heavy metal as is practised in Britain Hill, Platou and Kometani (1947) as a result of considerable investigation upon the effects of penicillin on the rate of healing of early infantile osseous syphilis, found that the drug temporarily accelerated the healing in infants treated during the first 3 months of life but that no such effects were produced in infants treated during the next 4 months in fact, they state that increase in severity may occur during penicillin treatment Pseudo-paralysis, which was present in 15 infants at the beginning of treatment, disappeared within 3 weeks in 12 of the patients and all 15 had cleared within a month. It was found that with penicillin periosteal changes persisted for quite a long time, just as we found to be the case with the older treatment with arsenicals and bismuth. I know of no large series of bone and joint cases in late congenital syphilis which had been treated mainly with penicillin by which the relative values of the modern and older lines of treatment might be compared.

Finally one may add that the serological reactions may be resistant in these bone and joint patients, and although the final stages of reversal of the W R. may take perhaps a year or even 2 years before a definite negative is obtained with the blood, we have usually been successful in reversing the W R. of patients who persevered with their treatment under arsenic and bismuth or mercury

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THE BLOOD IN CONGENITAL SYPHILIS

Congenital syphilis was formerly a widespread and often an intense infection in young infants, hence it is not surprising that many sufferers from the disease showed evidence of a mild or severe anaemia.

The liver spleen and bone marrow function as haemopoietic organs from comparatively early in foetal life, and they may all be involved in congenital syphilis. All the haemal structures, red cells, leucocytes and platelets may be affected in syphilis as they may in any severe infection in infants or children. There is nothing distinctive about the anaemia of congenital syphilis and the haematological findings must therefore be correlated with the clinical manifestations.

The anaemia may result from interference with haemopoiesis or from a haemolytic process. The former may be due to a toxic or vascular disturbance in the bone marrow to specific inflammatory changes involving the bones, osteochondritis or osteomyelitis, or to a secondary iron deficiency leading to a hypochromic anaemia. In many cases a combination of causes may be operative. McLean (1931) noted the association of anaemia with severe osseous involvement 20 infants with haemoglobin values of less than 50 per cent all had severe bone lesions, and 15 of them died while under observation We have been able to confirm McLean's findings in a number of our own cases.

There are considerable differences of opinion as to the incidence of anaemia in syphilitic patients. Lange (1919) found 18 of his 100 patients anaemic. Piney (1932) says that congenital syphilis is almost invariably associated with changes in the peripheral blood. We were unable to make a routine examination of the blood in all our patients, and examined only those who were obviously or probably anaemic. They comprised not more than one-quarter of all our patients, though it should be stated that our material did not include many syphilitic neonates to the age of 1 or 2 months the age at which many of the patients were wont to succumb to the severity of their infection.

In considering the blood changes in congenital syphilis it will be convenient to refer to three different age periods

(1) from birth to 6 months,
(2) *from 6 months to 2 years,*
(3) from 2 years upwards.

(a) Lymphocytic type

The anaemia may be of a specific type in the younger patients, and is to be related to toxic and granulomatous interference with the bone-marrow activity In the infants under 6 months it is associated with a normocytic

anaemia with relative lymphocytosis but only moderate hepatosplenomegaly Also seen in children under 2 years of age is a syndrome of anaemia and gross hepatosplenomegaly similar to that described by von Jaksch. Hypochromic anaemia may occur at all ages due to iron deficiency and associated in infants with the not infrequent prematurity and in the older children with general ill health, poor diet and lack of appetite. It is likely that there was a haemolytic element in many cases but the means at our disposal for its recognition were primitive compared to those in use to-day however one case of probable haemolytic anaemia will be described. Bismuth therapy apparently caused or aggravated the anaemia in some of our patients and an illustrative case report is given below

Generally speaking it was found in infants from birth to 6 months of age that there was a reduction in the number of red blood corpuscles and in the amount of haemoglobin, an increase in the number of leucocytes which were, as is usual at this age, predominantly lymphocytes, and in addition a variable number of nucleated red cells and myelocytes were found in the peripheral blood Our patients in this group varied in age from 2 to 5 months, the haemoglobin ranging from 20 to 52 per cent, and the leucocyte count from 14,000 to 18 000 per c.mm. with 63 to 91 per cent lymphocytes. One of our patients who had numerous circulating nucleated red cells died at the age of 3 months, whereas three other patients who had none survived. This variety of anaemia is normochromic in type and characterized by a considerable lymphocytosis I would call this the *lymphocytic type* Primitive red and white cells may occur in the peripheral blood and it may be related to interference with bone marrow activity either of toxic origin or by specific osseous lesions. It is of interest to recall that Stuhl described a case of congenital syphilis which presented clinically as one of lymphatic leukaemia in a neonate, the infant dying on the seventeenth day Post mortem, miliary syphilomata were found in the liver as they were in our fatal case mentioned above.

In 1890 von Jaksch described a condition the chief features of which were a reduction in the haemoglobin and red blood corpuscles with marked aniso- and poikilocytosis, numerous nucleated red cells in the peripheral blood and a marked leucocytosis with relative lymphocytosis. His cases showed considerable enlargement of liver and spleen and moderate lymphadenopathy The condition is sometimes known as *anaemia pseudo-leukaemica infantum* it is to be regarded as a syndrome of varying aetiologies rather than as a specific disease entity and congenital syphilis is undoubtedly one of the predisposing causes. Our cases described above had similar haematological findings to von Jaksch s patients but lacked the gross enlargement of the liver and spleen. We have, however had a further 5 cases with anaemia and marked hepatosplenomegaly although the leucocytosis was less conspicuous in some of

them than is usual in pseudo-leukaemia infantum. The ages of our patients ranged from 4 weeks to 17 months 2 who were under 6 months died, the other 3 responded poorly to antisyphilitic treatment and required both iron and blood transfusion In one of them the anaemia was aggravated by over-enthusiastic bismuth therapy and is discussed further in a later section.

(*b*) The second variety of anaemia might be called the *nutritional* or *secondary* (*hypochromic*) type. This type may occur at any age we had cases under 6 months, between 6 months and 2 years and over 2 years. Similar cases may be met with in non-syphilitic children, but as a rule not under the age of 6 months

(1) Syphilitic infants under the age of 6 months suffering from this type of anaemia usually died from the severity of their infection and it is possible that the modern treatment with penicillin may prove more successful than did the former treatment with arsenicals or heavy metal in curing this type of case

(2) Between 6 months and 2 years we had several cases, some with only 20 or 30 per cent haemoglobin and several of them did not respond to usual haematinic treatment until they had been given one or more blood-transfusions.

(3) This type of anaemia in children over 2 years was found to be usually associated with attacks of paroxysmal haemoglobinuria.

In the treatment of these cases it is important to give not only antisyphilitic therapy but also adequate treatment with iron and transfusions when indicated

The difficulties in the recognition of a haemolytic element in the production of this anaemia in our patients have already been pointed out One of our patients was studied by Hawksley who recorded the case (1934) as being one of splenic anaemia and congenital syphilis. Review of the findings in the light of more modern haematological interpretation suggests that there was hypersplenism leading to haemolysis, associated possibly with blood loss from oesophageal varices. The history was as follows.

The mother was infected almost certainly at the beginning of her pregnancy with this patient. The infant snuffled at birth and at 3 months had a rash on the arms and legs and X-ray but no clinical epiphysitis. Her blood and C S F were positive at that time and the former became negative 4 months later after one course of bisoxyl (10 injections = 5 3 ml.). At 8½ months the head was bossed and rather rachitic in appearance and the liver and spleen were enlarged. At 13 months the child had cut only 3 teeth. Bisoxyl injections were continued and by the age of 17 months she had become markedly anaemic. The hepato- and splenomegaly especially the latter persisted and the patient was admitted to the ward under Dr Thursfield for detailed haematological study This gave the following results

R.B.C. 1,800,000. Hb 35% C.I 0·96.
W.B C. 6 300. Reticulocytes 3·7%.
Differential Lymphocytes 50%
Polymorphs 39%
Monocytes 6%
Eosinophiles 3%
Myelocytes 1%
Myeloblasts 1%
Normoblasts 2 per 100 W B C.
Van den Bergh reaction Indirect pos. 1 unit.
Fragility test Complete haemolysis in 0·36% trace in 0·48% NaCl.

Hawksley studied the patient for 3 months, doing blood counts twice weekly and concluded from the clinical and haematological picture that the condition was essentially that called splenic anaemia, and he added it must be assumed that rarely congenital syphilis can produce this syndrome. As the child's anaemia did not respond to the treatment given, splenectomy was decided upon. The appearance of the liver and spleen at operation was similar to that seen in advanced cases of splenic anaemia and hepatic cirrhosis. Ascites occurred after the operation and was still present when the child left hospital 5 weeks later it had disappeared when the case was reported 3 months after the operation. The prognosis was regarded as poor on account of the cirrhosis of the liver and the fact that the blood count remained subnormal. The child died some months later—it is said "from a chill"—and as this occurred at home without our knowledge no post-mortem investigation was carried out.

Many of our syphilitic patients were treated by injection of bismuth in the form of bisoxyl Mild toxic manifestations with casts and albumin in the urine were encountered from time to time and sometimes a blue black line appeared on the gums. However it was also observed that some patients developed an anaemia during the course of treatment, the pathogenesis of which is obscure and needs investigation. The history of one case has just been given in which it is an open question whether the anaemia was due to the congenital syphilis or the result of overdosing with bismuth. The following patient developed a severe anaemia of the von Jaksch type after treatment with large doses of bismuth. He made a good recovery after treatment with blood transfusions and iron.

This child, Freddie C., had been treated at another hospital from the age of 4 months with 12 weekly injections of 1 ml. bisoxyl which was in my opinion far too big a dose for an infant of his age. This information was only obtained subsequently when, on our treating the patient with rather smaller doses of bisoxyl, he developed albumin and casts in the urine a progressive anaemia, enlargement of the liver and spleen with ascites, several attacks of epistaxis and pyrexia to 104 F This all happened when he was about 18 months old. The blood count gave the following results

R.B.C 2,000,000 per c.mm. Haemoglobin 15–20%
W B.C. 11,000 per c.mm. C I 0·4.
Halometer reading 7 32
Poikilocytosis, anisocytosis, polychromasia and punctate basophilia were present.

Differential leucocyte count	Lymphocytes	72%
	Polymorphonuclears	27%
	Monocytes	1%

12 nucleated red cells were seen while counting 100 leucocytes.

At a previous count 1% myelocytes were present. The patient was given 3 transfusions (100, 130 and 150 ml.) during the ensuing 17 days, after which the blood improved to R.B.C. 3·6 millions and the haemoglobin to 60%. The administration of reduced iron completed the treatment and the boy eventually made a good recovery. When last seen at the age of nearly 8 years he was doing well but his head was still rather big and broad and his eyes somewhat prominent. The blood W. R. had been negative since he was 2 years old and the C.S.F. was negative at 9 and at 16 months.

The use of organic arsenicals in the treatment of congenital syphilis may lead to aplastic anaemia or to agranulocytosis, but we did not encounter this in our series of cases.

Erythroblastosis foetalis

The discovery of the Rh antigen in 1939 and of the consequences of Rh group incompatibility between the mother and foetus has afforded an explanation of a number of curious conditions leading to stillbirth or encountered in the newborn. It has been shown that the diffusion of antibodies through the placenta may lead to the birth of a macerated foetus with a cirrhotic liver or a baby with hydrops foetalis that may be stillborn or die within a few hours. In other cases associated with incomplete antibodies the baby may be normal at birth but develop a haemolytic anaemia sometimes associated with icterus gravis neonatorum, within a few days. These apparently dissimilar conditions have apparently the same underlying cause and are now grouped together under the heading of erythroblastosis foetalis.

It was formerly believed that a woman who suffered several miscarriages or stillbirths was syphilitic, and even if her W. R. was negative she was frequently given antisyphilitic treatment in the attempt to enable her to bear a living child. This treatment was frequently unsuccessful and, in the case of women whose W. R. was negative, usually so. It is probable that many of these cases of repeated stillbirth were due to blood group incompatibility rather than to syphilis, but it is important to realize that hydrops foetalis is sometimes of syphilitic origin. Gilmour (1944) has reviewed this subject and has described the histological features which may help to distinguish between erythroblastosis foetalis and congenital syphilis. He mentions that in congenital syphilis much of the haemopoiesis in the portal system and kidneys is lymphocytic and that plasma cells may be found in these sites. Macroscopically the metaphyses of the long bones showed changes indicative of a deepened zone of provisionally calcified cartilage in both diseases but in congenital syphilis there may be

in addition evidences of osteochondritis such as fibrosis of the metaphyses and of the enlarging chondral canals and other changes mentioned under bones (see p 191) Henderson (1942) in comparing the two diseases states, among other points, that the placenta may be enlarged in both and that histologically there is a superficial resemblance between the two diseases in the presence of enlarged villi and diminished vascularity Other similarities are the extra medullary erythropoiesis and hepatic cirrhosis in both conditions. Henderson disagrees with Gilmour Caffey and other observers about the presence of osteochondritis or osteochondrosis in erythroblastosis foetalis.

It is obvious that the two conditions are not easily distinguishable and it is practically certain that they may coexist in the same patient (Gilmour 1944, Hawksley and Lightwood 1934). It is probable that true erythroblastosis foetalis is always due to blood group incompatibility between the mother and foetus, but Gilmour (personal communication, 1946) is of the opinion that congenital syphilis may predispose to erythroblastosis when there are any group differences, by increasing the permeability of the placenta.

It is the tendency nowadays to regard all cases of hydrops foetalis and icterus gravis neonatorum as being due to erythroblastosis foetalis. It has already been pointed out that congenital syphilis may result in hydrops foetalis, and it is even more important from the therapeutic point of view to remember that congenital syphilis may give rise to icterus gravis neonatorum Gilmour in his review quoted above, describes 3 cases of syphilitic origin The following reports from our clinic give details of 2 cases of infantile jaundice. The first was associated with severe anaemia and responded rapidly to treatment.

The patient was the only survivor of triplets, the fellows having died at birth and at 6 days respectively When seen at the Surgical Outpatients Clinic at the age of 2 months, the symptoms were snuffles and jaundice and the signs were a big head with enlarged scalp veins. The blood examination showed R.B.C. 2·8 millions W.B.C., no record of the total number but differential lymphocytes 61%, polymorphs 19%, monocytes 17%, eosinophiles 2%, plasma cells 1%. Punctate basophilia was present. The W R. was positive at 6 months and became negative by 11 months after one course of 8 bismostab injections (4 8 ml.). Radiograms of the bones were negative at 9 months and the C.S.F at 1 year He was well when last seen at the age of $3^{10}/_{12}$ years, having received 51 ml. bismostab in 44 injections spread over 2 years and 7 months. Treatment was irregular as the mother had 3 other children to care for and she lived several miles (at least 10) from the hospital. He had furnished 7 negative serological blood tests from the age of 11 months.

The second case was seen and described by Hawksley and Lightwood (1934) in their paper on erythroblastosis foetalis.

The infant, a female of syphilitic parentage, was born prematurely at 7 months with a rash. When seen at the age of 14 days she had syphilitic pemphigus,

osteoperiostitis jaundice with enlarged liver and spleen and a syphilitic "wig. The W R. was positive in both parents and patient. She died with convulsions at the age of 4 weeks. The post mortem findings were stated to be those of congenital syphilis. In the liver the capillaries were engorged the columns of cells being widely separated. The sinusoids contained large numbers of megaloblasts, erythroblasts and normoblasts. Bile pigments had been deposited in the cells and bile capillaries. The bile ducts and portal tracts showed no fibrosis. The spleen was congested and showed obvious haemopoiesis with deposition of bile pigment. The cortex and medulla of the adrenals were congested with much haemopoiesis in the medulla.

Both these patients presented clinical features pointing to a syphilitic aetiology but it is important to seek evidence of parental and familial syphilis in cases of icterus gravis neonatorum in addition to studying the blood groups of the family

Changes in the erythrocyte sedimentation rate (E.S.R.)

Shortly after the E.S R. test was introduced into practical medicine and stated by Weiss (1928) to be of value in unmasking latent cases of congenital syphilis, we took steps to utilize the clinical material at our disposal and with little extra trouble the E.S R. could be tested at the same time as the W R. by taking the blood for both tests in one syringe It was found that the sedimentation rate was increased in many untreated congenital syphilis patients and usually the rate diminished with treatment and the consequent improvement in the patient s condition

We invariably employed Payne s method (1932), in which citrated blood (1 part 3 8 per cent neutral sodium citrate to 4 parts of blood) is taken up into a narrow tube to a height of 100 mm. The reading is taken at the end of one hour and a settlement of corpuscles above 10 mm. is regarded as abnormal. We made 288 observations on 69 syphilitic children 65 congenital syphilitics 2 who had acquired the disease in early life and 2 children free from symptoms whose mothers were themselves syphilitic. Of the 65 congenital syphilitic children 35 were under 1 year and it was usually found that a high sedimentation rate betokened a severe infection and that a satisfactory therapeutic response to treatment (either injections of arsphenamines, bisoxyl or oral stovarsol) was paralleled by a reduction in the E.S R. For example, an infant of 3 months with snuffles, rash and marasmus whose E.S R. was 65 mm. registered only 35 mm. 6 weeks later after 4 bisoxyl injections, and 9 weeks after that having received a course of sulphostab the E S R. had fallen to 6 mm Another infant also 3 months old with snuffles, rash and splenomegaly had an E.S.R. of 71 mm. which 3 months later fell to 37 after 9 injections of bisoxyl After more bisoxyl injections and 4 of sulphostab (0 8 G) she developed a severe arsenical dermatitis, so that the E S R. was not tested for nearly one year It was then found to be only 13 mm. and was finally 8 mm. a

years and 3 months after it was first tested A third infant who had no infantile symptoms of congenital syphilis was taken to another children's hospital at the age of 4 months on account of marasmus. It was then discovered that he had a positive W R. and he was transferred to our clinic for treatment. When we examined him his only objective symptoms were otorrhoea and a failure to thrive. We were able to confirm that his W R. was positive and his E.S R. was 72 mm. There was no clinical epiphysitis but by X ray all the long bones showed well marked periostitis, which probably accounted for the high sedimentation rate. After 7 bisoxyl injections (2 4 ml.) the W.R. was nearly negative and the E S.R. had fallen to 24 mm. after 9 further bisoxyl injections (5 4 ml.) the W.R. was negative and the E.S R. had fallen to the normal figure of 10 mm. 7 months after we took the first tests

The sedimentation rate does not always follow such a progressively favourable course as the above recorded 3 cases exhibited, as is shown by the following case

W.D., born in 1936 was the third child of his parents, and like the 2 older sibs is said to have been healthy at birth. The 2 older children had latent syphilis when we examined them the W.R. being positive in both children with the E.S R. 5 mm. in the girl aged 5 years and 23 mm. in the boy aged 2 years. They both showed signs of old choroiditis with partial secondary optic atrophy The third child after being well at birth developed unequivocal signs of congenital syphilis—rash and snuffles—at the age of 5 weeks, and when we examined him at 7 weeks he had a rash on the buttocks and legs, peeling hands and feet and X ray evidence of epiphysitis. His E.S.R. after 4 bisoxyl injections was 51 mm. and 3 months later after 6 more bismuth injections his W R. had become negative and the E.S R. had fallen to the normal 10 mm. He then began to show signs of rickets and some months afterwards, although the W.R. was still negative and the rickets was showing signs of healing, the E.S.R. was 33 mm. Six months later after an attack of pneumonia, the E.S.R. was still raised (25 mm.), and 9 months after he was very chesty and the sedimentation rate was 35 mm.

This case illustrates the fact that a raised E.S R. is not a diagnostic sign of congenital syphilis, but is an additional sign which may be of prognostic value if it shows a progressive lowering On the other hand, it may later become raised again if complications arise, as they did in this case (acute rickets and pneumonia) or a jump from normal to 66 mm., as we saw in another (an acquired) case, due to tonsillitis, with a temperature of 102 F the week previous to the determination of the E.S R. In both cases the W R. had reversed to negative and remained negative although the E.S.R. was raised. In our experience the E.S R. was not invariably much raised in infants, for in a patient 3 days old, who was suffering from syphilitic pemphigus, we found the E.S R. only 14 mm., and in untreated infants of 3 and 5 months the sedimentation rate was 8 and 12 mm. respectively

A raised E.S R. which does not fall in spite of antisyphilitic treatment

may be of bad prognostic import, as the following case appears to show

J C. was seen at 3 months suffering from frank congenital syphilis. She had no clinical epiphysitis, but on X ray examination all the long bones showed very marked periostitis, including some of the metacarpal bones. The W R. was strongly positive and the E.S R. was 65 mm. After a course of bisoxyl (5 5 ml.), which would normally produce marked clinical improvement and reverse the W R. the latter became only slightly less strong and the E.S R. rose to 72 and then fell somewhat to 53 mm. The infant had a bout of pyrexia, a bronchitic cough and died at 8½ months.

A child of a syphilitic mother who had received some treatment during her pregnancy was free from the disease and at 9 months her E.S R. was 5 mm. This is what Weiss found and is what one would expect to occur yet the E.S R. may be raised owing to some complication, as in the following case

The child of a syphilitic mother who was treated during pregnancy showed no evident signs of the congenital disease and gave 7 negative W R.'s from 5 weeks to 21 months of age, had an E.S.R. of 26 mm. at 5 weeks with a rash (? pemphigoid) on the head and neck at 9 weeks the rate had increased to 53 mm., when the infant had many more septic spots, and reached a peak of 55 mm. during an attack of pneumonia, with a temperature of 105 F at 13 weeks. Thereafter the rate fell slowly at 4, 8½ and 15 months to 30, 27 and 17 mm. and reached a normal figure at 21 months, when the child looked very well and showed no signs of congenital syphilis.

In children over the age of 1 year a high E.S R. is much less frequently met with than in infants. The highest figure we obtained was 50 mm in a girl of 11½ years with synovitis of both knees, showing no osseous changes by X ray Five and 7 months later after stovarsol neo-arsphenamine and bisoxyl the figures were 4 and 5 mm respectively The next highest figures we obtained were 44 mm. in a boy aged 7½ years suffering from infantilism and with an open fontanelle 37 mm in a girl of 4½ years who had no signs of active disease but a positive W R. who showed the typical facies of a congenital syphilitic, and whose left nostril was practically occluded by scar tissue from early ulceration. After treatment with sulphostab and bisoxyl the E.S R. improved from 37 mm. to 25 20 and 12 mm. in 4 months, though the W R. was then still strongly positive.

A few of the remaining patients over 1 year of age had a slightly raised E.S.R. (15 23 and 33 mm.), but at later tests the rates had fallen to normal The main points of interest from our observations were

1 The E.S R. was not raised in patients with latent syphilis and therefore was not of any assistance in diagnosing latent syphilis, as was suggested by Weiss.

2 It did not appear to be of much or any help in the diagnosis of latent neurosyphilis in the absence of signs of active disease A boy of 9 with

primary optic atrophy and a positive C.S.F had an E.S R. of 4 mm A girl of 8 with latent neurosyphilis and a history of interstitial keratitis had an initial E.S.R. of 15 mm. and 5 subsequent normal rates during a period of 21 months of intensive treatment, with a positive C S F the whole time. A girl of 12 with latent neurosyphilis had a normal E.S.R. for about 18 months, when it suddenly shot up to 45 mm., and slowly returned to normal during the ensuing 3½ years. The only possible explanation of the sudden rise to 45 mm. was toxic action on the liver of a somewhat intensive course of treatment with arsenicals, for at the previous W.R. test the patient's serum was bile-stained, though the E.S R. was only 2 mm. The C.S F was positive until the patient was 16 years old. The next case was a brother of the previous one and also a latent neurosyphilitic, though not so strongly positive in the C.S.F as the sister He was suffering from active congenital syphilis in the form of paroxysmal haemoglobinuria with secondary anaemia. His first E.S.R., after a little treatment at another hospital, was 33 mm. and this was followed by 8 38 35 14 and 11 mm. during the ensuing 17 months.

3 Two patients, aged respectively 4½ and 6 years, had normal E.S R. s although both had paroxysmal haemoglobinuria, so that the raised rate in the boy mentioned in para. 2 may have been due to his anaemia or to his neurosyphilis and probably not to the haemoglobinuria.

4. Finally we did not think that the E.S.R. had the prognostic value in children over 1 year which it apparently may have in children up to the age of 12 months.

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Paroxysmal Haemoglobinuria

Of the numerous unsolved problems of syphilis possibly one of the most interesting is the condition known as paroxysmal haemoglobinuria. Although the first authentic case described in 1854 by Dressler under the

title A Case of Intermittent Albuminuria and Chromaturia occurred in a congenitally syphilitic boy of 10½ years, it was 50 years before the pathological basis of the condition was discovered independently by Donath and Landsteiner (1904) and by Eason (1904–6), and several years more before it was generally recognized that congenital syphilis was by far the most common cause of the syndrome. Even to-day after nearly 100 years, there are still unexplained factors, especially as regards the relation of paroxysmal haemoglobinuria to immunity reactions in syphilis and the type of case in which the syndrome occurs

Definition

After exposure to cold which may give rise to an attack of shivering or to a genuine rigor the susceptible individual experiences pains in various parts of the body and on the next occasion when he or she passes water finds it to be dark-coloured even as dark as port wine The urine on examination is found to contain very few or even no red blood corpuscles, thus distinguishing the condition from haematuria, and the fact that these attacks of haemoglobinuria may recur periodically on exposure to cold has earned for the condition the name paroxysmal haemoglobinuria *a frigore* or paroxysmal cold haemoglobinuria.

Historical

Several English physicians between the years 1865 and 1884 (Harley Dickinson Gull, Pavy Greenhow Legg and S. Mackenzie) described cases of repeated attacks of haematuria under the names *intermittent haematuria* or *haematinuria* Pavy in 1866 first suggested the name paroxysmal but he called the condition haematuria, and the name *paroxysmal haemoglobinuria* appears to have been given to the condition for the first time by Secchi in 1872 Stephen Mackenzie and Boas wrote papers on the disease under the heading paroxysmal haemoglobinuria in 1883 and for the next 50 years the condition continued to be known by that name In comparatively recent times however other types of paroxysmal haemoglobinuria have been recognized and this particular condition is now usually qualified by the term syphilitic. The majority of the early English cases occurred in adults, and although a history of syphilis was given in a few of them most of the patients appeared to have been benefited or cured by quinine and their haemoglobinuria was almost certainly of malarial origin It must not be forgotten that at the period to which we refer malaria or ague, as the condition was usually called was not at all uncommon in certain parts of this country

Regarding the connection of haemoglobinuria with syphilis, Legg wrote in 1874 The presence of syphilis has been noted in a few of the cases,

but in most of the recorded cases nothing is said about a syphilitic taint. Lichtheim, Murri, Ehrlich S Mackenzie, Boas, Küssner and others all reported cases in syphilitic patients but these were almost all adults. Götze (1884) described a case in a congenitally-syphilitic girl of 9 who showed Hutchinson s teeth, nodes on the tibiae and double interstitial keratitis.

In the year 1902 Fagge and Pye Smith s Textbook of Medicine stated that of late years several cases had been reported in which haemoglobinuria followed syphilis. The disease was said to be much more common in men than in women and most apt to occur in young adults, but might continue up to the age of 40 or 50 Even as late as the year 1908 Sir John Rose Bradford, writing in Allbutt and Rolleston s System of Medicine on paroxysmal haemoglobinuria, which he included under the General Pathology of the Renal Functions, makes no mention of syphilis amongst the causes of the condition However in the same year Still (*loc cit.*, p 317) stated that paroxysmal haemoglobinuria in children usually if not always, indicated parental syphilis, and that he himself had notes of 4 cases in which there was evidence of syphilis in either the children or the parents. The condition being relatively more frequent in children than in adults it is not surprising that paediatricians were the first to recognize the association of paroxysmal haemoglobinuria with congenital syphilis In 1903 Leonard Guthrie, during a discussion at a meeting at which a patient with Raynaud s disease was shown, said he regarded paroxysmal haemoglobinuria and Raynaud s disease as different expressions of the same state, and the former in children was almost entirely due to congenital syphilis. He referred also to two sisters under his care with marked stigmata of congenital syphilis, who both had paroxysmal haemoglobinuria. Both these astute clinicians, Guthrie and Still based their conclusions upon clinical and anamnestic grounds, for the Wassermann test was not elaborated until 1906 too late to influence Guthrie, and Still was very sceptical of the value of the test as performed at that time.

Moss (1911) studied 3 cases, a coloured boy and girl 7 and 8 years old respectively both congenital syphilitics, and a white male aged 32, possibly a congenital syphilitic, in whom the attacks started at 23 In the same year Grafe recorded a case in a congenitally-syphilitic boy of 10 In 1912 Kumagai and Inoue studied 20 cases in Japan where the disease was apparently not so rare as in other parts of the world Of their 20 cases, 7 had acquired syphilis 10, aged from 6 to 42, were congenital syphilitics while the remaining 3 aged respectively 14, 24 and 49 years, had positive Wassermann reactions and no other symptom or sign of the disease. Matsuo, also in Japan, recorded 11 cases of paroxysmal haemoglobinuria seen by him in the year 1911 7 and possibly an eighth case, were congenital syphilitics the other 3 were acquired

In 1913 Browning and Watson stated that in 59 recorded cases the W R. was positive in 53 (90 per cent) Of their 6 personal cases, 5 were children aged from 2½ to 8 years, all of whom had congenital syphilis (one with a negative W R.) while the sixth case was a man of 24 with a history of acquired syphilis. They were convinced of the syphilitic basis of paroxysmal cold haemoglobinuria and showed that the Donath Landsteiner and Wassermann reactions assisted in strengthening their conclusion. Henceforward most authorities concurred in this view and later observations have borne testimony to the soundness of Browning and Watson's observations.

Pathology

The opinions of the earlier writers upon the pathology of paroxysmal haemoglobinuria are well outlined by Chvostek in his monograph upon the subject published in 1894. A critical review by Mackenzie (1929) carries the subject from the era of speculation up to and beyond the years 1904–1906 when Donath and Landsteiner and Eason independently demonstrated that the primary cause of the condition was the presence in the blood of an amboceptor a haemolysin, which possessed the peculiar property of sensitizing the red blood corpuscles in the cold so that when they were warmed up haemolysis occurred The haemolysis can be demonstrated *in vitro* and it occurs also *in vivo* when, if sufficiently intense, it gives rise to haemoglobinuria

It was early realized that the condition was different from haematuria, inasmuch as practically no red cells were present in the freshly voided urine The colour of the urine was attributed to unaltered blood pigment or to haematin, but, as Lichtheim was the first to point out, the urine was transparent and not smoky or opaque as it is in haematuria.

The occurrence of intravascular haemolysis in paroxysmal haemoglobinuria was first demonstrated by Kussner (1879). In a patient whose first attack of haemoglobinuria occurred at the age of 59, he showed that the serum obtained by cupping was of a ruby red colour during an attack, while between attacks it was pale amber-coloured. Rosenbach (1880) showed that in a susceptible individual an attack of haemoglobinuria could be induced by immersing the patient's feet in ice-cold water for 10 minutes. This is still frequently used for diagnostic purposes under the name of the Rosenbach test.

Ehrlich (1881) was also interested in the pathology of the condition. He found that if an elastic band be applied round the finger of a haemoglobinuric patient, and the finger then chilled for 15 minutes and warmed for an equal time, blood taken into a capillary tube and allowed to clot shows the serum tinted red. In a normal person no such abnormality is found.

During the ensuing 20 years little further progress was made than the mere recital of similar cases and of their association sometimes with vasomotor disturbances.

In 1903 Eason of Edinburgh began his observations upon the pathology of the condition, and in 1904 Donath and Landsteiner published their first communication upon the subject. They showed, firstly that the serum or plasma of these patients contains a lysin having the property of being able to combine with the red blood corpuscles at low temperatures (though the actual temperature varies in different cases) Secondly that the haemolytic reaction takes place in two stages, (1) the union of lysin with the red blood corpuscles at the low temperature, which may be called the *sensitization of the red blood corpuscles* and (2) *lysis of the red blood cor* puscles on warming the mixture. Thirdly that complement is essential for the second phase of the reaction.

Although the main outline of the reaction affords a correct explanation of what takes place in this condition, many subsequent observations have shown that it is not an invariable rule. Browning and Watson (1912 1913) and Matsuo (1912) among others found that considerable variations occur in the action of the lysins."

Moss (1911) and Dennie and Robertson (1915) carried out further work on the mechanism of the Donath Landsteiner test, and a possible explanation of the difficulties encountered was given by Yorke and Macfie a work published in 1921 They found that the longer the red blood cor puscles were exposed to the cold, the more sensitized cells there were present for the complement available with the result that there was less haemolysis with the blood kept at 0 C for ½ to 1 hour than for 5–7 minutes only This is an important observation which should be repeated but apparently has so far not been done, for it may well explain some of the discrepant results recorded by different observers

Bearing in mind the reservations in the interpretation of the test, the best method of carrying it out is that of Sanford as given by Whitby and Britton.

There seems to be considerable difference of opinion as to the amount of blood which may be lost in this condition Rose Bradford (1908) mentions that even half the total number of corpuscles may be lost," whereas Dennie and Robertson (1915) estimated that the haematuria following a moderately severe experimental exposure to cold resulted in the destruction of only approximately 6 3 ml. of blood. It is likely that only a small fraction of the haemoglobin liberated in the destruction of the red blood corpuscles will escape through the kidneys into the urine, although possibly in this condition the renal threshold for haemoglobin may be abnormal. Gilligan and Blumgart (1941) reported certain studies in cases of March haemoglobinuria, in which they estimated that about 10 ml. of red cells had been haemolysed in the course of a

normal attack, and they found definite evidence of a low renal threshold for haemoglobin.

An interesting point in connection with this haemolysin is that it may be present in long-standing cases of syphilis without the patient having haemoglobinuria thus Donath and Landsteiner found haemoglobinuria in 6 out of 65 cases of general paralysis, and Kumagai and Inoue in 20 per cent of cases of tabes and other late syphilitic manifestations. It seems that the haemolysin is produced in a number of patients and that under certain conditions but not always, it may give rise to destruction of the red corpuscles. Whether this ambocepter (haemolysin) is derived from the treponema or from the patient's own tissues is still a matter of speculation it appears to be different from the amboceptor or reagin upon which the Wassermann reaction depends.

Among the cases reported during the closing years of the last century it appeared that acquired syphilis was as common as the congenital form in giving rise to this symptom. Admittedly paroxysmal haemoglobinuria is now a rare manifestation of syphilis and there appears to be no doubt that it is more common in the congenital form of the disease than in the acquired. Harrison, who during his 40 years experience of venereal disease must have seen thousands of cases of syphilis, informs me that he cannot remember having seen more than two or three cases of paroxysmal haemoglobinuria, and he cannot remember whether they had any Raynaud symptoms. He has also informed me that his friend Dr Clements, who had a 30 years V D experience could not remember one case of the condition So also Anwyl Davies, who in a 25 year practice in V D clinics can recall only 4 cases of paroxysmal haemoglobinuria, of which 2 were in congenital syphilitics. None of his cases presented Raynaud symptoms.

As regards the type of case in which haemoglobinuria occurs, it appears practically always to be in a case of congenital syphilis which is otherwise latent in other words, there are no other manifestations of the disease present (Becker 1948) The same applies to many cases of interstitial keratitis, which has led some authorities to look upon haemoglobinuria as an allergic phenomenon as many regard interstitial keratitis at the present day

Clinical manifestations

Between the years 1912 and 1939 we encountered at the *Hospital for Sick Children* Great Ormond Street, 13 cases of undoubted paroxysmal haemoglobinuria in congenitally syphilitic children. In addition, there were 5 other cases, 3 possible instances of this condition and 2 patients who had paroxysmal haemoglobinuria and a complement fixation reaction (W R) which was thought to be a "false-positive" Brief case-histories of these 5 atypical cases are given at the end of the chapter The full clinical details are given in Table 12

Family history In our 13 cases, investigations of the parents revealed the following data

Fathers (13)

5 were old soldiers who had been out East.
2 W R. positive.
3 W.R. negative.
1 refused W R.
2 not seen.

Mothers (13)

4 congenital syphilitic or probably so
6 W R. positive.
1 died previously but had a syphilitic history
2 were not seen or not tested.

There were two points of interest about the parental histories in these cases. The first is the high incidence of congenital syphilis seen in the mothers, to which attention does not appear to have been drawn in the past. The other point of interest is that the parents infection had often occurred many years before the child was born, suggesting perhaps that it had become relatively avirulent or burnt out, thus explaining its tendency to give rise to a comparatively late manifestation of the disease as the first sign of a syphilitic taint in the offspring

There are a few instances of familial cases recorded in the literature, although we have not encountered any in our series. Herringham (1886) had 2 sisters affected with the condition Guthrie (1903) also had 2 cases in sisters, and Matsuo (1912) reported a family in which the father the daughter and 2 cousins were affected.

Patients' early and subsequent history It is clear from the table that, with the exception of a single case and possibly a second one, there is a complete absence of infantile symptoms of congenital syphilis, and similarly once this manifestation of the disease had been satisfactorily treated, it was not common for other changes to appear subsequently although in 2 cases interstitial keratitis developed (one with iritis), and a third case showed the remains of old choroido-retinitis On the other hand 5 of our children showed at least suggestive and, in some cases typical Hutchinsonian characteristics of their permanent teeth when these were subsequently erupted.

Age and sex The age at which our patients had their first attack ranged from 1½ to 6¼ years. Among the youngest cases on record in the literature is Wiltshire s patient (1867), who first developed the attacks at the age of 7 months. It is not possible to get help from earlier records to indicate the oldest age at which the condition may appear because after the age of 20 the differentiation from acquired syphilis becomes increasingly difficult.

Patients with Paroxysm

Case and sex	First attack Age Date	Previous symptoms	Family history	Symptoms and signs of attack: Exposure to cold	Paper R., or slower neg. S.	Pain	Other symptoms or signs
1 ♀	4 11/12 X.1920	No infantile sy. Rickets since birth.	F. Old soldier "bad leg." W.R. not done. M. W.R. not done. Sibs. W.R. positive	Yes	No	Lower abdomen and before micturition.	—
2 ♀	1 1/12 III 1922	No infantile sy.	F. W.R. and K. neg. M. Probably congenital. W.R. 4×4.	Yes	R.	Headache	Tired in legs. Became thin
3 ♂	3½ I.1924	Snuffles.	F. W.R. 4 4. No history of sy. M. W.R. 4 4. Patient only child.	Yes	No	Stomach, back of head, legs.	Attack every day. Liver and enlarged.
4 ♀	4 12 X.1926 ? earlier	None recorded.	F. Not seen. M. W.R. 4 4.	Yes	?	?	
5 ♀	3½ III 1925	No infantile sy.	F. History of sy. 1903. M. Infected 1906 W.R. 4 4.	Yes	R.	Legs ache	Anaemic. Spleen and liver enlarged
6 ♂	4 1/12 XI. 1933	No infantile sy. Delicate baby	F. W.R. neg. M. Died cong. G.P.I. Br. Syphilitic.	?	?	?	
7 ♂	1 XI 1925	Infantile sy. treated with mercury for 3 mos. only	F. An old soldier. M. W.R. 4 4.	Yes	R.	None	
8 ♂	5½ XI 1933	No infantile sy. Undersized.	F. W.R. neg. M. Cong. neurosyphilis. Sabs. 3 blood W.R. pos. blood and C.S.F. pos.	Yes	No	?	
9 ♂	2 XI 1929	No infantile sy. Jaundice at 3 yrs.	F. Refused test. M. Cong. G.P.I. (see p. 306).	Yes	S.	None	Jaundice. Two attacks of palpitation
10 ♂	1 III 1933	No infantile sy.	F. An old soldier. M. Not tested.	Yes	R.	None	Vomiting. Spleen enlarged. Febrile during attack
11	6½ XI 1932	Early history unknown. Both parents dead	F. Died G.P.I. M. Said to have had sy.	Yes	No	None	Anaemic
12 ♂	1 X.1917	No infantile sy.	F. Not tested. M. W.R. weak pos.	Yes	R.	Hypogastrium ½ hr. before haemoglobinuria	
13 ♂	4½ I.1935	No infantile sy.	F. An old soldier. W.R. neg. M. W.R. strong pos., one mons., had two neonatal deaths.	Yes	No	None	Anaemic

12

Haemoglobinuria

Treatment				
Treatment given	*Effect on haemoglobinuria*	*Effect on W.R.*	*Later symptoms*	*Remarks*
Arsphenamine 12 g G, six courses in 3½ yrs., mercury iodide.	Cured after first course.	Neg. at 8 and till 12 9/12 yrs.	Anaemia, squint, Hutchinsonian teeth.	
Arsph. 10 G. mercury iodide.	Cured after first course; "can go out in all weathers."	Neg. at 6 and to 8½ yrs.	None to 9 yrs.	Not treated until 4½ yrs
Pot. iod. and hyd. [illegible] oint. for [illegible] yr; arsph.; mercury iodide, bismuth and Bismuryl, stovarsol.	No cure with mercury; attack 6 mo. later. No more attacks after injections started	Neg. at 3½ yrs	Hutchinsonian teeth, I.K. during tr. and relapse later with neg. W.R.	The year's tr. with pot. iod. and Hg did not benefit the pt.
Arsph.; mercury iodide, two courses.	No further attacks while attending (9 mo.)	Neg. at 5 9/12 yrs.	None in next 9 mo.	Defaulted
Stovarsol.	No attacks after treatment started	Still + + when defaulted at 9 yrs	Choroido-retinitis, Hutchinsonian teeth.	Donath–Landsteiner test neg. Rosenbach test pos.; became neg. after 3 weeks tr.
Bismuryl 36 ml; sulphostab, 10 G.; mercury iodide.	No further attacks after bismuth.	Neg. at 8½ yrs	Anaemia, mild [illegible], Hutchinsonian teeth (H 1–2)	
Arsph., four courses; mercury iodide.	No return of symptoms after treatment started.	Relapsed once, finally neg. at 6 yrs.	Fibrotic tonsils at 6½ yrs. Hutchinsonian teeth (H [illegible]).	Tr. irregular; defaulted at 8 yrs. W.R. neg. then
Bismuryl 18 ml; arsph. 4.5 G.	Cured by treatment	Neg. at 7½ and till [illegible] yrs	None	C.S.F. W.R. pos. Family R. see p. 402.
Arsph. 8.3 G.; mercury iodide.	Cured by injections.	Reported neg. at [illegible] yrs.	Grew slowly	Blood count, red cell fragility, liver function tests and C.S.F. found normal at Westminster Hospital
Arsph. 8.7 G., mercury	Cured by one course. Mother once or twice suspected attack but none occurred.	Still pos. when transferred at [illegible] yrs.	Transferred, subsequent history unknown	First seen at 8 yrs; has admitted to surgical wards at H.S.C. No tr. for [illegible] as no symptoms while in hosp.
Arsph. 12 G. bismuth, mercury iodide.	Cured by first injection	Neg. at [illegible] relapsed at 3 and 5, Kahn pos. at 16 yrs	Cervical gland enlarged at 6½ yrs. and keratitis after much tr. at 9½ yrs.	Both parents said to have been infected 7 yrs before patient's birth.
Arsph. 10.4 G. Mercury	Attack the day after first inj. Rigor but no haemoglobinuria after two. Cured by first course.	Neg. after 18 mo. treatment at 7 11/12 and till 8 yrs.	Deaf at 14½ probably followed otorrhoea at 8 yrs	Started in [illegible], no attacks summer 1938, recurred Oct. and [illegible] att. winter 1938–9, Oct. 9–Jan. 1940, 5 att. April 1940, 4 att. on successive days. Tr. started May 1940.
Bismuryl, one course, later irregularly	Cured.	Neg. at 7³ ; and several relapses till 9 yrs. [illegible] last seen.		

In our cases the sex distribution is 7 males to 6 females. This is similar to Matsuo's distribution in congenital syphilitic patients—3 males to 4 females. On the other hand, it is obvious from the early reports in the literature, many of which concerned patients with acquired syphilis, that in that form of the disease the male sex is predominantly affected

Symptomatology Mackenzie, in the review already referred to in which he describes 3 additional cases of his own says that the clinical manifestations may vary considerably the first sign being usually the passage of dark urine. The exposure to cold may be slight and there is great variation in the amount of chilling necessary to bring on an attack. In fact in one of Mackenzie's patients numerous attacks occurred in bed in a well heated hospital in New York in July! The interval between exposure to cold and the haemoglobinuric attack may vary from a few minutes to several hours. In our patients the attacks nearly always began in the autumn or winter and were associated with exposure to cold. In several of the cases the attacks ceased during the warmer months of the year to come on again in the late autumn.

In several of the reported cases it was stated that a rigor and a rise in temperature to 102 to 104 F preceded the passage of dark urine. Mackenzie, however stated that cases may occur without either chill or fever Lichtheim as long ago as 1875 suggested that the mechanism of the rigor was the liberation of the contents of the red blood cell into the circulation In our cases in only 3 patients was it possible to obtain a history of true rigors, although in 3 others the mother said the child shivered felt cold and often turned blue before the attack came on Raised temperatures were only occasionally recorded in our cases one or two of the patients vomited in the prodromal stage. At this time also a few complained of generalized body pains in the back or in the legs and occasionally of headache Two had pain over the bladder which was relieved by the passage of bloodstained urine.

Several authors have noted that abortive attacks may occur either as (1) haemoglobinuria without the constitutional disturbances (chills, fever headaches) or (2) typical constitutional symptoms without haemoglobinuria and during such attacks the patient may have a transient haemoglobinaemia Such a condition was seen in several of our patients during the course of treatment and the mother was wont to say that on account of the constitutional symptoms she had expected the child to pass dark urine but that it had failed to do so

Browning and Watson (1912–13) found that later attacks might be more readily produced than the earlier ones, that they tended to occur at shorter intervals and to be of increasing duration Our own observations do not bear this out. Among other symptoms noted by these authors were yawning, drowsiness and stretching in the prodromal phase.

Two of our patients had mild attacks of jaundice in association with

episodes of haemoglobinuria. This has also been noted in a number of reports in the literature. The development of anaemia during a series of haemoglobinuric attacks has also been referred to in a number of reports, and 3 of our children became anaemic. One of them showed moderate enlargement of the liver and spleen and similar visceral enlargement occurred in another patient without the development of anaemia. It is not possible to say with our present lack of knowledge of the amount of blood destroyed, whether this anaemia may be attributed to haemolysis or whether it is to be regarded as part of a concomitant action of the syphilitic process on the bone marrow Unfortunately full haematological studies were only carried out on one patient in our series and in that patient when the anaemia was most severe the haemoglobin was 51 per cent, the red cell count 3 million per c.mm., white cell count and differential count were normal reticulocytes were 2·2 per cent.

Raynaud's phenomenon

A study of the accounts which have been published of Raynaud's disease during the past century leaves little doubt that some form of vasomotor disturbance is not an infrequent accompaniment of the haemoglobinuria in some cases it is referred to as a vasomotor disturbance, in other cases as Raynaud's phenomenon or Raynaud's syndrome and sometimes it is indicated that gangrene of the digits, nose or ears has occurred. Murri (1879–85) was of the opinion that vasomotor disturbances were the cause of the haemoglobinuria but there has been little confirmation of this from subsequent investigators. A number of writers have noted that urticarial reactions are not uncommon in these cases (Lichtheim 1876 Mackenzie 1884, Herringham 1886) Sir Thomas Lewis (1936) has clarified the position with regard to the confusion of nomenclature which has arisen in attempts to describe the vasomotor disturbances. It is quite clear that the classical Raynaud's phenomenon with local syncope, followed by cyanosis and occasionally by gangrene, and due to abnormal sensitivity to cold of the small arterioles, does not occur in this disease. He has pointed out that the commonest disturbance accompanying the haemoglobinuria is an urticarial reaction to cold He has demonstrated that a dermolysin is present comparable to the haemolysin which in the presence of cold unites with the skin cells and causes these to break down when the part is warmed Dependent on the degree of injury to the tissues and particularly to the endothelium of blood vessels in the skin, one may get as a result either urticaria in which the fingers may be swollen and white or oedematous, or one may get gangrene or in less severe cases, cyanosis of the extremities. This dermolysin is capable of passive transfer and causing local disturbances if injected into the skin of a normal person who is then exposed to cold. It must be emphasized that these vasomotor changes do not show the characteristic evolution of Raynaud's phenomenon

and that designation should probably not be applied to them. Our experience in this respect has been unusual. We have encountered no cases in which either urticarial or gangrenous changes have occurred. One of our patients did develop gangrene of the toes, but it is unlikely that this was a classical example of paroxysmal haemoglobinuria, and a fuller report is given as No 14 in the atypical cases at the end of the chapter

Special investigations

In all our 13 cases of undoubted syphilitic paroxysmal cold haemoglobinuria, the Wassermann reaction was strongly positive. In most cases it became negative on treatment and the details of the results are given in the table. The Rosenbach test was performed in only one case (No 5) in which it was positive and became negative within 3 weeks of starting treatment. The Donath-Landsteiner test was only carried out on one occasion, also in Case No 5 and was negative by the technique in use at that time.

Differential diagnosis

The most important point in the diagnosis of this condition is to bear in mind the possibility of its occurrence and this applies particularly to the patient who has been admitted to a surgical ward. The isolated passage of a red urine frequently suggests the possibility of a surgical disturbance, and it is not uncommon for extensive investigations, including often cystoscopy to be performed when a patient is actually suffering from haemoglobinuria. Other causes of red urine may lead to confusion it may occasionally follow the consumption of beetroot, it may be due to porphyria, but by far the commonest cause of confusion is between haemoglobinuria and haematuria. Naked-eye examination may help to differentiate these two conditions, because whereas in the former the urine is clear in the latter it has a smoky appearance. Microscopic examination of the sediment should be performed as soon as possible. In haematuria the urine will be packed with intact red blood corpuscles whereas in haemoglobinuria only occasional red cells will be seen in numbers quite out of keeping with the colour of the urine and, in addition, there may be occasional casts. Spectroscopic examination will confirm the presence of oxyhaemoglobin and will usually also show the spectrum of methaemalbumin.

Once it has been established that the patient is suffering from haemoglobinuria, the performance of the Rosenbach test the Wassermann reaction and the Donath Landsteiner test should point to the most likely cause of the condition Should these tests give negative results other possibilities would have to be considered. A severe haemolytic anaemia of the acute Lederer type may occasionally be associated with haemo-

globinuria. Also intravascular haemolysis, produced by such poisons as arseniuretted hydrogen and by favism, may give rise to the condition March haemoglobinuria may be confused with the syphilitic variety but a correct history indicating its association with exercise rather than with cold and the fact that it occurs in an otherwise healthy young adult man should render the differentiation comparatively easy Nocturnal haemoglobinuria of the Marchiafava-Micheli type will rarely be expected to cause difficulty in the differential diagnosis of a patient of this age. Paroxysmal myoglobinuria is another extremely rare condition which must be included in the differential diagnosis.

In recent years haemolytic anaemias, haemoglobinuria and vasomotor disturbances in the extremities have been described in association with the presence of cold agglutinins in high titre in the circulating blood. Salen (1935), Benians and Feasby (1941), Stats and Wasserman (1943) and Becker (1948) have all published accounts of this condition and its recognition. The Donath Landsteiner test may be expected to be negative in haemoglobinuria associated with a high titre of cold agglutinins, whereas correctly performed by the technique indicated above, it should be positive in most cases of the syphilitic disease. Study of the family history and performance of Wassermann reaction on parents and siblings will also help to recognize a syphilitic taint. The patient's W.R. is possibly not reliable in cases of this type. High titres of cold agglutinins are often associated with high plasma globulin levels and occur in a number of conditions in which false-positive Wassermann reactions have been recorded. Two cases recorded at the end of this chapter (Nos. 17 and 18) are possible examples of this condition, although they were not so recognized at the time. These patients had nothing to suggest a syphilitic origin for their disease either in their personal or family histories. The parents Wassermann reactions were negative. Nevertheless, the children themselves had episodes of haemoglobinuria and had transient positive Wassermann reactions There do not yet appear to be any cases on record in which false positive reactions have been found in association with haemoglobinuria due to cold agglutination, but it is possible that our two cases were of that nature.

Treatment

We have found any form of antisyphilitic treatment given by injection to be satisfactory in these cases. Clinical improvement usually followed the first or second injection and it was certainly manifest by the completion of the first course of treatment. To one or two patients we gave stovarsol by mouth this usually led to a fairly rapid clinical cure, but the Wassermann reaction was not rendered permanently negative. A number of the earlier reports in the literature have suggested that paroxysmal haemoglobinuria is comparatively resistant to treatment. Our results are

certainly not in agreement with these findings, and they are confirmed by Mackenzie, Browning and Watson, and others who found that intensive treatment invariably led to clinical cure and, as Mackenzie pointed out, the clinical cure occurs first, then the Wassermann reaction becomes negative and finally the Donath Landsteiner test becomes negative. In future, cases of this disease will undoubtedly be treated with penicillin, and there are one or two records already available of adults with the acquired disease in whom a clinical cure has been obtained following penicillin therapy. As yet, however the follow up is not sufficiently long to confirm that the cure will be permanent (Goldberg 1947 Becker 1948)

Atypical Personal Cases

Ivy P., age 10. Admitted to Great Ormond Street Hospital in 1919 under Fairbank. She had no history of infantile syphilis and her mother's W R. and those of her three sisters were negative. The patient was mentally defective and had a spastic paraplegia her blood W.R. was strongly positive and although the cerebrospinal fluid was not examined she had undoubtedly cerebrospinal syphilis of the general paretic type. Mr Fairbank performed an orthopaedic operation on both thighs to try and relieve the deformities of the diplegia and subsequently the patient on several occasions passed a red urine and developed gangrenous areas on both feet. The operation was performed in October 1919. It is possible that the haemoglobinuria and gangrene were a direct result of the operative interference rather than a syphilitic process. One course of arsphenamine was given and there was no more haemoglobinuria. The patient was subsequently transferred to an infirmary and was lost sight of

In the absence of much more investigation it does not seem profitable to speculate on the aetiology of this patient's haemoglobinuria and gangrene, and there is certainly not sufficient evidence to include her among the typical cases.

The following patients give typical histories of the passage of red urine unfortunately the records do not include a definite statement that microscopic examination had been performed and had excluded the possibility of the condition being one of haematuria. Although in all probability these were cases of haemoglobinuria they have not been included in the main table.

Vera G had her first attack of blood in the urine in 1912, when she was 4 years old. Her parents could not be interviewed, so that we have no record of any infantile symptoms of syphilis. She passed blood in the urine on and off for 3 years between the ages of 4 and 6 and on admission to hospital she was found to be mentally defective and to be suffering from spastic diplegia. She had no "haematuria" when she was under observation. Her Wassermann reaction was strongly positive and after one course of arsphenamine injections she was transferred to a mental hospital when she was subsequently lost sight of

Kenneth G a first attack occurred at the age of 4 years in August 1930, when he had blood in the urine for a week. There was no oedema or any other symptoms and there had been no infantile symptoms of syphilis. The boy's Wasser

mann reaction was strongly positive, as was that of his mother and a younger sister had died of congenital syphilis. His Wassermann reaction became negative in 7 months on bismuth alone and he subsequently had 5 negative tests to the age of $12^{4}/_{12}$ years. After treatment was started he had no recurrence of the haematuria (or haemoglobinuria).

The following two cases have already been discussed in the text under the heading of differential diagnosis Both apparently came from families which were free from syphilis, but both showed transient positive Wassermann reactions and episodes of haemoglobinuria. Although the other tests, such as the Donath-Landsteiner and cold-agglutination tests, were not carried out, it appears not unlikely in retrospect that the haemoglobinuria in these cases might have been due to cold agglutinins and the Wassermann reaction results false-positives."

Mary U was 9 years old in 1928. In May of that year she had an appendicectomy performed and in August and September she had three attacks of painless haemoglobinuria. The Wassermann reactions in the mother and father were negative and her 6 brothers and sisters were stated to be healthy but did not have blood tests performed The patient's W R. was strongly positive on two occasions and then without any treatment two negative results were subsequently obtained.

Charles P was admitted to the ward at the age of $3\frac{1}{2}$ under the care of Dr Robert Hutchison. He had measles when he was $2^{11}/_{12}$ years old and shortly before admission to the ward in December 1923 he had a cold and sore throat followed a week later by the passage of bloodstained urine. It was at first thought that this was due to a glomerular nephritis. Microscopic examination of the urine showed that although a few casts were present, the number of intact red cells was quite out of keeping with the colour of the urine and spectroscopic examination showed the bands of oxyhaemoglobin and methaemoglobin. Five days later *a further attack of haemoglobinuria occurred and 2 days after that a* further slight one He had a weakly positive W R. on one occasion and subsequently 6 negative tests until he was nearly 6 years old. W R. of both parents were negative. He was given 16 injections of arsphenamine and tablets of mercury iodide, after which no further attacks of haemoglobinuria occurred.

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The Lymph-nodes

In Chapter 5 it was stated that the *T pallidum* travels by way of the lymph spaces and lymphatics, particularly the perivascular lymphatics to the regional lymph-nodes and via the blood stream throughout the body Lymphadenitis may therefore be present in congenital as it is in acquired syphilis, but the glands are rarely so large in the infant with the congenital disease as they are in the acquired disease of the adult. In the congenital syphilitic infant the epitrochlear gland is frequently palpable Hochsinger and others believed this to be associated with epiphysitis of the lower end of the humerus, which is possible but difficult to prove The inguinal, occipital and axillary glands may also be slightly enlarged from the size of a small shot to that of a haricot bean, and in the absence of an obvious cause, such as a skin lesion the presence of enlarged glands should arouse a suspicion of congenital syphilis. Lymphadenitis is, however of very limited diagnostic value at this early age for it may be absent in frank cases of infantile congenital syphilis and on the other hand, it may be present in non-syphilitic patients.

In older congenital syphilitics enlarged lymph-nodes are not infrequently present, but they are usually diagnosed as being tuberculous. Still quotes the case of a 6-year-old boy with a large nodular tumour of the groin which subsided under antisyphilitic treatment. Jonathan Hutchinson described the case of a girl of 15 years with interstitial keratitis and greatly enlarged cervical glands which responded rapidly to treatment with iodide of potassium Weill Bertoye and Bernheim (1923) described a case of late congenital syphilis of the lymph nodes which resembled Hodgkin's disease. Histologically giant cells, endothelial proliferation and changes in the blood vessels were present. Cappell (1936) has drawn attention to the similarity between the lymphadenopathy of syphilis and tubercle, and to the inherent difficulty in histological diagnosis

The finer points in the differential diagnosis have long been recognised by morbid histologists, but to the average microscopist the presence of multinucleated cells in sections of a gland denotes tubercle. So too with clinicians. Enlarged glands, particularly in the cervical region are considered to be due either to infected tonsils or to tuberculosis without any or with but a fleeting thought of any other cause of enlargement such as syphilis or other granulomatous condition. The expert clinician while realizing that by far the commonest causes are tubercle and sepsis will

take steps to establish the diagnosis, such as doing a Mantoux test and a leucocyte count. Should these be unhelpful he would carry out a Wassermann test and in the last resort perform a biopsy on a gland to diagnose between tubercle, syphilis, the Hodgkin syndrome and neoplasm.

We come now to the consideration of lymph node enlargement in our series of patients. Since the majority of syphilitic infants show a variable degree of lymph-node enlargement, in assessing the value of this sign in syphilitic children, infants below the age of 6 months have been left out of consideration. We encountered at least 46 children over the age of 6 months among our syphilitic patients in whom the glands were considered enlarged, between 5 and 6 per cent of the total. These we have divided into two groups A and B.

> Group A, comprising *14 patients in whom the presenting symptom was enlargement of the glands and who showed no other manifestation of congenital syphilis* although they may have had early infantile symptoms of the disease and
>
> *Group B*, comprising *32 patients in whom other manifestations of congenital syphilis* in addition to the enlarged glands, *were present*.

Group A, though the smaller of the two groups is from the practical point of view the more important, since when the patients were first seen their syphilis was of the latent or silent variety in fact quite quiescent.

Brief details are given of a few of these cases.

Beatrice C. was admitted to the Children's Hospital under Mr Tyrrell Gray for enlarged glands in the neck at the age of 10⁵/₁₂ years. The mother had died 6 years previously after a mental illness which had lasted some years (probably general paralysis). The patient is said to have had no infantile symptoms of congenital syphilis and on examination her teeth and eyes were normal her only complaint being enlarged glands in the neck which had been present for a considerable time, but exact duration uncertain. The child was brought to hospital by her eldest sister who was 10 years her senior and an obvious victim of congenital syphilis with characteristic facies (rhagades teeth and saddle-nose) and interstitial keratitis.

The patient's enlarged glands were thought to be possibly lymphadenomatous. There is no record of a Mantoux test being done. The blood W. R. was found to be strongly positive. Antisyphilitic injections were started but the patient's attendance was very irregular so that she had only 4 injections (1 G. neoarsphenamine) in all. When she was next seen at 12½ years of age, the glands *had subsided* but the W. R. was still strongly positive. 2½ years later the patient was very well and the W. R. was still positive—she had had no further treatment in the interval and, having taken up domestic service, she could not be persuaded to attend hospital again.

A sister to the above patient was 2½ years older. She likewise had no infantile symptoms of congenital syphilis and developed enlarged cervical glands,

especially on the left side of the neck for which she attended Dr Paterson's out patients clinic. Her teeth and eyes were normal and the patient had no obvious signs of syphilis. At the age of 12¹/₁₂ years she had a swelling of the head of the right fibula, painful for one day only There was no history of any injury and on X ray examination no changes were to be seen in the leg bones. The patient was treated with neo-silver-salvarsan (4.45 G) over a period of 15 months, during which time the glands subsided and there was no return of the bone trouble.

Frank F., born in 1912, had no infantile or later symptoms of syphilis but was vaguely below par during his school age From the year 1922 the London County Council had an arrangement with the Children's Hospital whereby schoolchildren who were notified by the school medical officer as suffering from "malnutrition" "debility" or as "not doing well" were admitted to the hospital for investigation, particularly from the point of view of hidden tubercle. This boy was admitted as such an L.C.C. case A radiological examination of his chest showed enlarged glands in the hila of both lungs but no evidence of active tubercle. The tubercle-complement fixation test was carried out with a negative result, while the "control" Wassermann was positive.

This gave the clue to the boy's debility the only other suggestive feature in the case being the history of the mother's one miscarriage at 4 months, 3 years before the birth of the patient. It was *subsequently* learnt that when the lad was about 8 years old his mother suffered from a ? gumma of the scalp her W.R. was found to be positive and both she and her husband received treatment at another hospital. Three older children were born before the parents became infected two of them were said to be well but they could not be induced to come for a blood test. The third one was suffering from a "rheumatic heart" at 16 years of age and her W R. was then negative. Our patient was given anti syphilitic treatment (17 G neo-arsphenamine in 42 injections and mercury iodide by mouth during 16 months), shortly after which the S.W R. became negative and the spinal fluid was found negative at the age of 12 years. The blood gave 9 further negative tests during the subsequent 4½ years. Despite the antispecific and adjuvant tonic treatment the boy received, he remained thin, pale and weedy The heart was rapid and irritable its impulse slapping, but no definite valvular lesion could be detected. At 15½ years he was working There is no available record of a Mantoux test, an electrocardiogram or of a second investigation of his mediastinal glands.

Four of the patients in this group resembled the above patient in being thought to be suffering from a tuberculous infection all 4 were certainly syphilitic and there was no evidence—bacteriological microscopical or radiological—that they were also tuberculous

Two young patients in this group were (1) A boy who at 1 year had a discharging abscess of the neck, which was thought to be possibly tuber culous in nature. No tubercle bacilli could be found in the scrapings from the abscess. (2) The other patient was a girl who at the age of 1 year had some cervical glands removed from the left side of the neck at her local hospital at 2 years she had an abscess in the right groin and at 5²/₁₂ years she again had left sided cervical adenitis which was thought to be due to tubercle or syphilis In neither of these two cases was the

tubercle bacillus discovered and the adenitis may have been gummatous in origin

Three patients in group A aged 4 or 5 years, had cervical adenitis to which septic tonsils may have contributed their quota with the syphilitic causation, for there was not much improvement in the glandular swelling as a result of antisyphilitic treatment until the tonsils and adenoids had been removed. In this connection it may be recalled that Hochsinger (1927) said that in older syphilitic children adenoid vegetations were apt to be unusually common and that the related cervical and submaxillary glands might be enlarged, which the unwary would probably diagnose as tuberculous.

The 32 cases of lymphadenopathy in group B included 6 patients ranging in age from 9 to 30 months In 4 of them the glandular enlargement was associated with septic tonsils. In the other 2 cases it was probably treponemal in origin one, a girl of 9 months, showed general lymph-node enlargement with periostitis, dactylitis, and a history of parotitis at 3 to 4 months the other a boy aged 18 months who after treatment with heavy metals (mercury and bismuth), during his first year quickly became serologically negative in blood and cerebrospinal fluid then developed cervical adenitis, probably indicative of a relapse of his infection, which manifested itself in an attack of alopecia and a serological relapse.

The other 26 cases in this group varied in age from $3^{4}/_{12}$ to 14 years. In 21 the glands affected were the cervical, anterior and posterior while in 3 others the original cervical lymphadenopathy spread to other regions later Of the 24 patients with cervical lymph-node enlargement, 8 had unhealthy or septic tonsils, and 6 had ulceration or gummatous disease of the pharyngeal wall and adjacent structures.

The remaining 2 patients had enlargement of the lymph nodes in other situations (1) A boy of 6½ years whose hilar glands were enlarged and mostly calcified, and had otherwise no sign of tuberculosis, but possibly fibrosis of the lungs (2) The other a boy of 4 who had had glands removed from the right groin at another hospital At 4¾ he was admitted to Great Ormond Street Hospital with an attack of meningitis which clinically and pathologically was thought to be tuberculous except that no tubercle bacilli were found in the spinal fluid, nor was a W R. done on the fluid. Upon the child recovering from his meningitis—and we had no streptomycin and para amino-salicylic acid in those days—it was realized that the meningitis was not tuberculous but probably syphilitic. The finding of a positive W R. gave support to this diagnosis and intensive antisyphilitic treatment was instituted (neo-arsphenamine and mercury iodide) During the attack of meningitis a mass had been felt in the right iliac fossa, and as this did not diminish in size under antisyphilitic treatment a biopsy of the mass was made which showed that the growth was malignant and probably a lymphosarcoma. The enlarged inguinal glands which, as

stated above, had been previously removed at another hospital, were no doubt due to the same cause. Despite X ray and radium treatment and further antisyphilitic injections, the lad went downhill and he died at his home at the age of $6^4/_{12}$ years. No further examination was possible. This was the only case we encountered in which congenital syphilis co-existed with malignant disease.

The most instructive of our cases with enlarged lymphatic glands, being as it was, the most carefully studied, was that of the girl Beryl F (mentioned on p 170), who had enlarged cervical glands from about the age of 3 years. She had sunlight treatment for 3 years and during this time she also attended an eye hospital for eye trouble (probably inter stitial keratitis) An older sister was attending the same eye hospital at the same time, but Beryl s eye affection was not correlated with the en larged glands. As these persisted after 3 years of sunlight treatment, the child was placed under the Tuberculosis Officer for 4 years, and as no active tubercle could be discovered she was sent to Great Ormond Street at the age of 10½ years. Here at the Outpatients Clinic the relevant facts noted were Anaemia, ? cause cervical adenitis liver + + + spleen not enlarged." Shortly afterwards the girl was admitted to the wards so that she could be more thoroughly investigated Several glands were found to be enlarged in the anterior and posterior triangles of the neck, in the submaxillary and infra and supra-clavicular regions. Two blood counts revealed a moderate degree of anaemia, haemoglobin 50 per cent, red blood cells 3 800 000 per c.mm., white blood cells 10 000 per c.mm. One of the enlarged cervical glands was removed for biopsy since lymphadenoma had been considered a possible diagnosis. The section of the gland was thought at the time to show typical tuberculous changes with characteristic giant cells, but no tubercle bacilli could be found. A Mantoux test was negative even with a 1 in 10 dilution of old tuberculin, O T., and it was considered unlikely that the gland could be tuberculous. The possibility of syphilis was then suggested and a blood test at the age of $10^4/_{12}$ years gave a strongly positive W R. and Kahn. The patient was given antisyphilitic treatment for nearly 3 years, but the cervical glands, although reduced in size, remained somewhat enlarged and she had a relapse of interstitial keratitis. The liver too, was still enlarged. The patient was obviously a neglected case of congenital syphilis in whom the lymphatic system had been severely implicated. Another physician, under whose care she was admitted to hospital 2 years later asked for a Mantoux test to be repeated, but even at the strength of 1 in 10 a negative result was again obtained. The sections of the gland were then shown to Professor Matthew Stewart, of Leeds, who was of the opinion that they were not tuberculous but syphilitic. He drew attention to the fact that the sections showed almost necrotic tissue, around which there was some better preserved lymphatic tissue containing multinucleated cells but no epithelioid

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cells as are usually to be seen in sections of tuberculous glands. He regarded the section as showing a gumma of a lymph node and Fig 82 illustrates the condition well and closely resembles the illustrations given by Cappell in his paper referred to above. Cappell there points out that the lesions in these syphilitic glands *may very easily be mistaken for tuberculous lesions*, but there are differences in structure which would arouse the suspicions of the more experienced observer such as peri and end arteritis, perivascular cell infiltration and necrosis of tissue with preserva



FIG 82 Gumma of lymph-node (300) Section of a cervical lymph node showing a number of multinucleated giant-cells which are surrounded by some endothelial cells plasma cells and lymphocytes. The Mantoux reaction (1 in 10 O T) was negative on 2 occasions

tion of structural outlines In the early stages of their enlargement such glands respond to antisyphilitic treatment *which would help in the diagnosis* In our case which was a very chronic one, the therapeutic response was not so satisfactory or so complete, for the patient still showed enlargement of various regional glands even when last seen at the age of 21 years.

These 46 cases of enlarged lymph nodes observed in about 850 congenital syphilis patients below adult age represent a percentage of about 5 5 at least 6 of them suffered from breaking-down or discharging glands, which were *possibly gummatous in nature*

In addition to the foregoing 46 4 other patients with enlarged lymph-

nodes were cases of acquired syphilis. One a boy of 7 years, in whom the posterior cervical glands were enlarged in syphilis supposed by the mother to have been acquired through an enema syringe. Another a girl aged 4 10/12 years, in whom the disease was contracted by sexual contact (see Fig 93). Her inguinal glands were enlarged and hard but they responded rapidly to antisyphilitic treatment. The other two patients were cases 10 and 11 given in Chapter 13 (p 443) in whom the regional glands were somewhat enlarged.

The moral to be drawn from our experience of lymph node enlargement in late congenital syphilis, although it may not be so applicable to-day as it was when our observations were made, is that in every case of subacute or chronic lymph-node enlargement, before a spot diagnosis of tuberculosis is made, as is so often the case, a tuberculin skin test and a W R. should be carried out, and in the event of these being negative or if the W R. alone should be positive, biopsy of a gland should be resorted to in order to diagnose between tubercle, syphilis, and the reticulo-endotheliosea.

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CHAPTER 8

SYMPTOMATOLOGY (*cont.*)

AFFECTIONS OF THE CENTRAL NERVOUS SYSTEM

THE affections of the central nervous system are the most important of all the manifestations of congenital syphilis. There are several reasons for this (1) they are often latent and if not actively looked for will remain undetected, to the serious detriment of the patient (2) they are much more common than is generally realized (3) if diagnosed in the latent stage before clinical neurosyphilis has declared itself and the condition is adequately treated there is a reasonable probability that benefit or even cure may result. If on the other hand, neurosyphilis is not diagnosed until it is clinically obvious, the chances are that by this time the condition is incurable and the patient is destined to become either a psychopath a permanent inmate of a mental institution, or a moral delinquent. In any event the unfortunate victim may become a considerable liability to the community and to the State, and one of the saddest aspects of congenital syphilis until recent times was to bear witness to the physical and mental degradation to which the young sufferers from this disease ultimately descended before death released them from their pitiable plight.

Incidence

Many observers (Ravaut 1903 1907 1934 Boas and Lind 1911 Wile and Stokes 1914–15 Fildes, Parnell and Maitland 1920 and others) have studied the effects of syphilis upon the C.N.S. of the adult, with the result that all are agreed that the C.N.S. is involved in at least 25 per cent of the patients in the early secondary stage of the acquired disease. Far fewer observations have been made upon the C.S.F. in congenital than in acquired syphilis.[1] Tezner (quoted by Ibrahim) found the C.S.F. abnormal in 62.5 per cent of syphilitic infants, 50 per cent with a positive W.R. Jeans and Cooke found changes in the spinal fluid in more than 50 per cent of their cases, which is in close accord with our own earlier figures from Great Ormond Street (53 per cent). The incidence of positive

[1] Early publications upon congenital neurosyphilis by Bresler (1904) Ravaut (1907) and others are given in the bibliography

neurosyphilis in infancy diminished as our investigations proceeded, for by the year 1939 when the list of new cases was closed 187 infants under 1 year of age had had lumbar puncture, with only 50 positive cases among those who had been treated for 3 months or less (26·7 per cent) Even if all the 32 patients who were examined after more than 3 months treatment and had negative spinal fluids had been positive at the outset, which is most unlikely the total 82 (50+32) of the 187 infants lumbar punctured would still be under 50 per cent (43 8) (Table 13). It is important to add that in a considerable proportion of these cases the condition is latent and would not be discovered except by the routine examination of the C.S.F in all cases of congenital syphilis (see also Lees)

The largest reported series of C.S F investigations in congenital syphilis is that of Jeans and Cooke (645 cases), an account of which is given in their book. They found that active neurosyphilis was twice as frequent amongst white infants as amongst the non whites, and that in older children the difference was considerably more marked one-sixth of the white children having neurological lesions, whereas only one sixtieth of the coloured children were similarly affected. This higher incidence of neurosyphilis is paralleled by the greater prevalence of tabes and general paralysis amongst adult whites than non-whites. Jeans and Cooke adopted as their essential criterion of neurosyphilis a positive W R. in the C.S F and they stated that the presence of globulin, slight pleocytosis and even an abnormal colloidal gold curve are not to be regarded as evidence of neurosyphilis, unless accompanied by a positive W R. Since that time those concerned in investigating the C.S F in syphilis have devised modes of grading the results. The Co-operative Clinical Group, U.S.A. (1937) classified the fluids into 4 groups according to the degree of abnormality of the 4 main tests (cells, proteins, colloidal gold, etc., and the W R.) and in their group 1 the W R. was negative. In 1942 Kierland and his co-workers suggested only 3 groups, mild moderate and severe, in the first of which the cells might be 10 to 20 the Nonne-Apelt reaction (N.A.) negative or increased the colloidal curve and W.R. negative. Lange and Harris (1945) introduced an improved method for performing and reporting quantitatively upon the gold-sol test, and Dattner (1948) has written upon the evaluation of the 4 important factors in the C S F examination (1) the cell count, (2) the total protein estimation, (3) the colloidal test, and (4) the complement fixation test These 4 tests Dattner considers obligatory (1) and (2) indicate activity (3) indicates the type of C.N S tissue involved and quantitatively gives the trend of the process, while (4) gives the specific nature of the disease and quantitatively gives the trend Whereas these gradings and inferences may be applicable to acquired neurosyphilis, my experience with the congenital form of the disease induced me to conclude that the gradings suggested for adults could not be applied to children (see Table 14)

Although a large volume of evidence has accumulated pointing to the frequency of the invasion of the C.N.S by the treponema and the serious potentialities of the condition, it is remarkable how frequently the investigation of the C.S F is omitted by paediatricians and sometimes even by venereal-diseases specialists. The reason often given is that lumbar puncture of children is not easy or to be lightly undertaken, although as a matter of fact if the child is properly held and the operation is performed upon a table or firm bed (preferably with a board placed under the mattress to ensure a correct position of the body and to prevent the bed sagging towards the midline) there is, as a rule, little difficulty in carrying out this minor operation if the usual precautions are taken. In the pre-penicillin era we considered it very important that the C.S.F should be examined in every case of congenital syphilis, since if it were found abnormal this was an additional reason for insisting upon the regular attendance of the child for treatment, which could only be reliably carried out by repeating the lumbar puncture every 3 months until it became permanently negative. Even in these days of the penicillin treatment of congenital syphilis it is advised that the spinal fluid be examined in every case and, if possible, before treatment is started.

Our series of C S F investigations was carried out on 640 patients, of whom about 600 were unselected cases of congenital syphilis, that is to say unselected from the point of view of neurosyphilis, the remainder being (1) children in syphilitic families whose blood W R. had been found negative either spontaneously or as a result of the mother's treatment before or during pregnancy and (2) some possibly acquired cases (see Chapter 13) at first regarded as congenital. Most of the lumbar punctures were performed after the year 1923 when small wards were provided in the Children's Hospital for the treatment of patients suffering from gonococcal and treponemal infections. Before that time one hesitated to do lumbar punctures upon outpatients, as many of them came from far afield, so that a number of the children investigated had already been attending the Clinic for from one up to several years, by which time the blood W R had become negative in many of the cases and there is no doubt that the treatment caused a number of positive spinal fluids also to become negative—how many it is impossible to say. The results of these spinal fluid investigations are shown in Table 13

In analysing the results one endeavoured to make them conform to the usually recognized gradings in acquired adult syphilis, but certain difficulties were encountered, notably a positive W R in the fluid in the absence of other changes or at the most, with only a slightly positive Lange curve. In consequence a somewhat different classification was adopted (see Table 14), and even this classification could not always be rigidly adhered to on account of dissociation or lack of correlation between the various components of the group-types. This dissociation is in my experience

TABLE 13

Results of C.S.F. Examination in 640 Patients (mostly Congenital Syphilitics), showing the Differences in Mortality according to the Age of the Patient and the Condition of the Fluid

Age	*No.*	*Results of first examination*		*Deaths from syphilis*	
		Positive	*Negative*	*Positive*	*Negative*
T 1 year	187	50 (4)[1]	137 (32)[1]	19 (38%)[2a]	18 (20%)[2a]
Over 1 year	453	87 (38)[1]	366 (186)[1]	8 (10%)[2b]	8 (2%)[2b]
Totals	640	137[3]	503 (18)[1]	27	26

Note [1] The numbers in brackets indicate patients who had been given treatment for more than than 3 months before being lumbar-punctured.

[2] The table shows (*a*) that the mortality is considerably higher below the age of 1 year than above that age, and (*b*) that over 1 year of age it is much higher in patients with a positive spinal fluid than with negative fluid.

[3] Amongst the positive cases the sexes were about equally divided 67 males, 70 females.

more marked in the case of congenitally syphilitic children than in the fluids of adult patients with acquired syphilis.

Other points of interest which emerged from the investigation of the 640 spinal fluids were

1 The number of latent and clinical neurosyphilis cases among the patients examined 47 patients with positive fluids showed no symptoms or signs of neurosyphilis and in addition there were 6 infants who may have had neurosyphilis, but in the absence of fits, hydrocephalus or obvious mental deficiency it was impossible to be certain 7 children showed only a slight or moderately strong W R., doubtless due to permeation, since the reaction rapidly became negative, and such cases were not regarded as being neurosyphilitic in nature 64 patients with positive fluids had signs or symptoms of clinical neurosyphilis, such as hydrocephalus, with fits, mental deficiency hemiplegia or paraplegias some of the last named were diagnosed clinically as spastic paraplegia or diplegia, or as poliomyelitis or polio-encephalitis. In addition there were 8 cases in which a mild hydrocephalus was the only sign, together with a positive C.S.F of clinical neurosyphilis. In 7 further cases with a positive C.S F the symptoms (' head nodding, mental weakness in the child of a mother with G.P I a cases of difficult children and a few others) suggested possibility of clinical neurosyphilis—together totalling 79 cases. In addition 37 children with epilepsy mental deficiency nystagmus and other signs of C.N.S. affection had a negative spinal fluid on the first examination but it is probable that if the patients had been lumbar punctured earlier in life some of them would have been found to have positive spinal fluids.

TABLE 14

Four types of Abnormal Cerebrospinal Fluids found in Congenitally-Syphilitic Children

Type of fluid	*Cells*	*Total protein*	*Nonne-Apelt*	*Lange colloidal reaction*	*Wassermann reaction*
1[1]	5 to 10 per c.mm.	To 0·05 % (=50 mg.)	1	With 1's or 2's only	Negative o.o. or W.R. +3 if no other abnormality than 1 or 2 in Lange's test
2	Up to 100 per c.mm.	To 0·1 % (=100 mg.)	1 or 2	1223332100	4.3.2.1
3	Up to 150 per c.mm.	To 0·15	2 or 3	1234432000 Luetic type	4.4.3.2.
4	More than 150 and up to 700 or more per c.mm.	From 0·15 to 0·4 %	4 or 5	4555543100 Paretic type	4.4.4.4. (4 4)

Note Dissociation is frequently present, total protein and globulin being unusually low in relation to the increase in the number of cells. On the other hand the cell count may be low usually with low protein content, while the Lange curve may be paretic in type and the W. R. strongly positive.

[1] Type 1 fluid is not regarded as evidence of neurosyphilis unless the W. R. shows some *degree of positivity in addition to a slight increase in cells and/or protein*

These findings may be summarized as in Table 15 bearing in mind the fact that the "positive" numbers are minimal for 218 of the patients had received more than 3 months' treatment before the spinal fluid was examined (see Table 13).

TABLE 15

Cases of Clinical and Latent Neurosyphilis among 640 Patients whose Spinal Fluid was Examined

Clinical Neurosyphilis

C.S.F. positive and signs or symptoms of neurosyphilis	64
" mild hydrocephalus	8
" miscellaneous signs or symptoms (see text)	7
Total	79
C.S.F. negative when first examined but neurological manifestations present (see text)	37
Total patients with neurological signs or symptoms	6

Latent Neurosyphilis

C.S.F. positive without signs or symptoms of neurosyphilis	47
Infants with positive fluids but no obvious signs of clinical neurosyphilis, called "latent"	6
Total latent or "latent"	53
"Permeation" cases—with only positive W. R.—regarded as being not neurosyphilis	7

2 The rate at which the various factors improved was found to vary in different cases but the cells almost always became normal before the other constituents of the spinal fluid, just as in the acquired neurosyphilis of adults. Usually the W R. remained positive much longer than did the other constituents, especially in older children. In 65 patients out of 137 in whom a positive fluid was found and in whom the necessary information was obtained, the C.S F became negative before the blood (usually m from 6 to 12 months) 49 times, simultaneously with the blood in 9 cases, and only 7 times was the blood negative before the C.S F It is generally believed that once a congenitally-syphilitic patient has given a negative reaction in the spinal fluid, it is unlikely ever to relapse. This does not accord with our experience, for 10 of our patients had spinal fluid relapses, 2 or 3 of them having had 2 relapses each. Since there may be a time lag, of as much as 5 or 6 months according to Jeans and Cooke, during which a child's spinal fluid develops a positive W.R. a C.S F which has been found negative before the age of 5 or 6 months should be re-examined for the presence or absence of neurosyphilis.

Table 16 gives a record of the varying types of spinal fluid found in our cases of infantile congenital syphilis, with comments. Cases 7 and 8 are interesting as occurring in infants 8 months old, both having slight hydrocephalus. In the one, the fluid was slightly opalescent, the protein 0·2 per cent, cells 190 to 200 (chiefly mononuclears), N.A. 4, Lange 4554341000 Wassermann 4 3 and no reduction of Fehling's solution. The other child gave a clear fluid, protein 0·03 per cent, cells 150 to 200, some polymorphs and endothelial cells, N.A. trace, Lange 2331000000 and the W R. 4.4. The first patient died very shortly afterwards and could therefore not be retested. At post mortem there were marked adhesions of the meninges at the base of the brain and the ependyma of the ventricles was granular The other patient, who had 9 repeat lumbar punctures until nearly 10 years of age, had practically normal protein cells 61 13 6 31 4, 3 6 1 and 2 N.A. varying between 1 and 2 until the last two tests, when it was quite negative. The W.R. remained strongly positive until the age of 5 and gradually diminished to negative at the age of 7½ years. The Lange remained at about the same strength until the age of 5 when it abruptly became practically normal. The boy defaulted at 12 years of age, when he was small in stature and mentally bright.

As regards the appearance of the fluid, it is usually clear and without any clot, but occasionally when there are many cells present it may be slightly opalescent sometimes it may show threads of clot and exceptionally there may be a yellowish tint, the result of previous haemorrhage. Case 5 exhibited these characteristics. This particular case also showed a high percentage of protein a marked Lange curve and very marked globulin content as shown by the N.A. 5 It should be noted that this patient, in spite of the indications of severe involvement of the C N S., had no

TABLE 16 Varying Spinal Fluids found in

Case and sex	Age	C.S.F. Date	C.S.F. Type	C.S.F. Character	Protein	Nonne-Apelt
1 J D ♂	(1) 3½ months ( ) 2 months	IX.32 III.34		Clear no clot. Ditto.	0.4 0 025	0 0
2. B G ♀	(1) 3 months (2) 6½ months	IV 34 VIII.34	2	Clear no clot. Very slightly blood-stained.	0 025 0 025	tr 0
3. D.B. ♀	(1) 3 months (2) years	IX.32 VI.34	0	Clear no clot Ditto.	06 0 025	1 0
4 D.B. ♀	(1) 8½ months (2) 1 ½ months	XII.33 IV 34	2	Clear Clear	03 02	1
5 I R. ♀	( ) 3 months (2) 6 months	VIII.33 IX.33	4	Yellowish, slightly turbid with small clot. Clear no clot.	0 2 0 3	5
6. F.H. ♂	( ) 5 months (2) 3 months	IX.24 II 25	2	Clear Clear	02 0 1	— ? tr
7 L.D. ♂	8 months	VI.25	3	Clear	0 3	tr
8 I W ♀	8 months	I.25	4	Slightly opalescent fluid.	02	4
9 O B ♀	3 months	VII 25	4	Fluid xanthochromic.	0 4	5
0 D R. ♂	( ) 6 months (2) 9 months	III.34 XI 34	2	Clear no clot Clear no clot	0 08 02	tr 0
1 B D ♂	( ) 6 months ( ) year (3) ½ years	III 36 II 37 III 37		Clear no clot Clear no clot Very slightly blood-stained	1 02 02	
2 N S	( ) year (2) 9 months	II 33 II 34	2	Clear Clear	08 025	
3 J K. ♂	months	III 33	4	Very slightly opalescent N let	6	2
4 S ♀	( ) 5 months (2) 20 months	X 26 29		Clear Clear	02 025	

Note ly = small lymphocytes. l.ly large lymphocytes poly polymorphonuclear leucocytes

our Cases of Infantile Congenital Syphilis

Cells per cmm.	*Lange*	*W.R.*	*Blood W.R.*	*Remarks*
8 ly	o–o ●–●	o.o. o.	4×4[1] o.	Latent neurosyphilis (?) Negative.
64 (50 ly) 8 (3 a.ly.)	233221000 —	4.o.o.o. o.o.	4×4 4 3 o.o.	Latent neurosyphilis. C.S.F went negative on Bismuryl alone between dates indicated.
50	1222333 00 o–●	4 4.o.o. o.	4×4 o.o.	Transient facial paralysis at 3 mths. Died at 2+ yrs. after splenectomy (see p. 24)
45	1233332 00 ●–o	4×4 o.o.	4-4 4 4 4 o.	C.S.F negative in 4 months on Bismuryl alone. *Nystagmus. Diffuse choroido-retinitis* and much [illegible] opacity latent neurosyphilis.
435 (90% a.ly.)	44555532 2332 00000	4×4 o.o.	4×4 4×4	*Latent neurosyphilis.* C.S.F negative in 3 months on Bismuryl alone (injections = 4 ml.). Died at 9 months Br.-pn. N p.m.
35 40	3 ●00000 o–●	4-4	4-4 and to 935	Treated with Hg and As in breast milk. At 3 months rickets and hydrocephalus. At ½ years head big with overhanging forehead. Wt. 8 at ? hypopituitarism. Spade hands. X-ray pituitary fossa —small.
50–200 (most ly a.ly., some l ly and polys.)	233 ●000●●	4-4	4×4	Hydrocephalus: head asymmetrical at 8 months. N other symptoms. At 8 months head smaller and of better shape. Blood and fluid remained positive for 5 years and only became negative after much treatment including malaria and tryparsamide.
95	45543 ●00	4-3	o.o.o.o.[2]	Oxycephaly. P.m. marked meningeal adhesions at base of brain. Hydroceph. ++ Granularity of ependyma of ventricles. Cerebral vessels and sinuses appear healthy. *Note S.W.R. negative. Child' mother congenital syphilitic.*
300	3455543322	4×4	4 4	Latent neurosyphilis but patient died at 3½ months of gastro-enteritis and no p.m. could be obtained sisters had positive C.S.F
44 5	●● 3422●00 ●●● ●00●●	4 4 o	4 4 4-3-o to	Hydrocephalus; snuffles, rash and X-ray epiphysitis alopecia.
(1 % poly) 80 (90% a.ly.)	32 000●000 ●1 ●000●●	4 4 4 o.o. o.o o.	4 4 4 4 3 4 2.o neg. Jan. 38 to Nov. 39	Monoplegia. M.D. Spasms. ? squint. Treatment given up at [illegible], yet blood and C.S.F W.R. had reverted to negative.
o●	o–● ●–●	4-4-4 3 o o.o.	4 4 o.o.	Patient had little treatment in infancy (at months). Hemiparesis at year. Diagnosed as Palsy.
670	223 ●000	4 4	4 4	Impetigo at months. Fits at 8 months. Hemiplegia at months blood. P.m. see p. 80.
3 5–30	32 ●00●● 222 000●0	4 4 o.	4-4 4 4	Mother congenital syphilitic. Patient had nystagmus and slight hydrocephalus. C.S.F relapsed second time at 3½ years. Note that the C.S.F was negative at 5 months with the nystagmus.

[1] W.R. strongly positive no haemolysis with serum diluted in 3 and in 30 and with 3 and 5 units of complement—my notation 4 4-4-4, or 4 4.
[2] This was the only case where blood W.R. was negative when C.S.F was positive.

neurological symptoms and the fluid became almost normal in 3 months on bismuth treatment alone. It is indeed remarkable how frequently the spinal fluid may show evidence of infection, sometimes even severe (vide also case 9) yet the condition is quite asymptomatic (latent or silent). Although this is not shown in the table, we found that in the large majority of congenital syphilitic spinal fluids sugar was present in normal amounts, thus differentiating these fluids from those obtained from patients with other forms of acute meningitis.

The conclusion that one has reached with regard to the grading of spinal fluids in congenital neurosyphilis is that it has but a limited value and from a diagnostic and prognostic point of view the C.S.F. findings must be correlated with the clinical condition. Furthermore, one examination of the spinal fluid is insufficient for prognostic purposes, and a pronouncement upon the outcome of the condition should be withheld until at least one course of treatment has been given and the spinal investigation has been repeated 3 months after the first test. Generally speaking one may say that if the second spinal fluid test shows a marked improvement in the cellular and protein content the outlook is good provided the patient is not obviously mentally defective or suffering from convulsions. A paretic type of Lange curve is usually regarded as being of sinister import and, with a few exceptions, this accords with one's own experience. Case 11 is an interesting one. The protein was never much raised, the cells were 80 per c.mm. at the first investigation, the C.S.F. W.R. became negative between the ages of 6 and 18 months, and the serum W.R. also rapidly improved and became negative before the child was 2 years old, yet his mental condition deteriorated to such an extent that by the time he was nearly 4 treatment was stopped as it was considered improbable that further treatment could serve any useful purpose. Such untoward results must depend primarily upon original damage to the developing nerve tissues and only secondarily and to a less extent, upon an extension of vascular disease leading to degeneration or destruction of the cerebral parenchyma, otherwise it is difficult to account for the fact that the W.R. became negative in the blood and C.S.F. and that the latter eventually showed no abnormality whatever.

In Chapter 5 (p. 87) it was stated that at one time we relied upon the paretic type of Lange curve for diagnosing the G.P.I. variety of neurosyphilis in young children. Table 17 shows 6 such or similar fluids, from which it is seen that 3 patients died quite young, while one survived to the age of 17 years with his syphilis inactive for several years but suffering from epileptic fits all the time. The other two patients were still alive at 16 and 31 years of age but both were suffering from epileptiform fits. On the whole, therefore, one's bad prognosis for infants and young children with paretic Lange curves appears to be justified, the question being whether the patients die in infancy or being cured of their active

TABLE 17

Results of the first C.S.F. Investigation in Cases of Neurosyphilis of G.P.I.-type in Infants and Very Young Children

Case and sex	Age	Date	Character	Type	Prot.	Cells	N. A.	Lange	W.R.	Blood W.R.	Remarks
1 P.L. ♂	11	20 VII 29	Very slightly 3 (?) chromatic, no clot	4	4	80 L	—	—	4+	4+	Died /12. Chlorides 7.6. No Tb. found. C.S.F. taken p.m. from cisterna magna.
2 V.W.	1	XII 28	Clear no clot		05	65 s.L.		—	4+	4+	Died ¹/₁₂. Meningo-encephalitis with ependymitis. Granulations in floor of 4th ventricle and elsewhere showed proliferation of glial tissue to such an extent that it actually burst through ependyma instead of pushing it before itself.
3 C.W.	2	VI 3	Slightly turbid	4		95	4	4334321 000	4 3+	n.o.	Died ⁹/₁₂. Granularity of ependyma of ventricles.
4 G.J. ♂	3[1]	VIII 24	Slightly turbid	4	5	18	—	4333432 00	4+ Relapse after having been neg. twice.	4+	Blood and fluid negative at 5 years, but fits continued and patient died at 7 years with no active syphilis.
5 M.H.	2 11	7 X 33	Clear no clot	3	05	50		43333422	4+	4+	C.S.F. negative in year S.W.R. neg. later. Mentally retarded and fits at 16 years.
6 A.M. ♂	2 11	20 II 5	Clear no clot	4	6	5	2	333432 000	4+	4+	C.S.F. neg. in 6 months. Still alive but epileptic at 3 years, doing useful work in an institution.

[1] During series of so-called epileptic seizures

Note: 1 mainly small lymphocytes.
1 died at 9, 3 and 9 months respectively. 4 died at 7 years, but cured of active syphilis. 5 and 6 were alive at 16 and 3 years respectively.

syphilis by much treatment yet remaining all the time so-called epileptics they die eventually it may be 30 or more years later with irreparable early damage to the higher intellectual centres.

Pathological anatomy

The anatomico-pathological lesions in congenital neurosyphilis are very varied and in the main resemble those seen in the acquired form of the disease. The commonest lesion is meningitis, either diffuse or a localized, gummatous form affecting the base and/or vertex of the brain and possibly too the spinal cord This may be accompanied by focal



Fig 83 A carotid artery from a male aged 11 months showing gross reduction in the lumen as the result of extensive intimal proliferation (90) Note that the elastic lamina is intact Elastic tissue stain

changes in the cerebral parenchyma which are doubtless due to vascular lesions, and not infrequently adhesions are found between the brain and meninges. In several cases we have seen the granular appearance of the ependyma of the ventricles present in children a condition usually associated with general paralysis in the adult. Early observers (Clifford Allbutt, Heubner Barlow and others) noted the frequency of syphilitic arterial disease, especially at the base of the brain, and of the small vessels of the brain and spinal cord Case 2 (J K p 276) is a good example of very marked syphilitic arterial disease in which the lumen of the vessels affected was almost obliterated, with resultant softening of the brain tissue (cysts, porencephaly). (See Figs. 83 84.) *The veins may be similarly affected* and their walls thickened by phlebitis. Haemorrhage may also result from

syphilitic disease of the vessels, so that occasionally a xanthochromic spinal fluid may be obtained on lumbar puncture, the result of bleeding during or shortly after birth, which is more frequent in syphilitic than in non-syphilitic neonates. In the more chronic cases the inflammation may go on to sclerosis of the brain and the varied clinical manifestations resulting therefrom will depend upon the site or sites of the lesions.

One of our cases was of particular interest

Peter L. had rash and snuffles from the first few weeks of life and seemed to improve on mercury treatment until about 5 months of age Then he began to ail and about 3 weeks before admission to hospital he began to make a "crowing noise in his throat." On admission to hospital under Dr Thursfield there



Fig 84. Necrosis of cerebral tissue (porencephaly) following upon a Herxheimer reaction affecting the posterior cerebral artery in an infant aged 10½ months

was a slight right facial palsy the arms and legs were spastic and the knee jerks increased. Nothing could be seen or felt in the larynx to account for the spasm. The C.S.F investigation (Table 17 case 1) showed marked evidence of neurosyphilis it was yellowish in colour cells 180 per c.mm. mostly lymphocytes, protein 0·4%, chlorides 7·6 sugar absent, no tubercle bacilli present and the W.R. strongly positive The child went rapidly downhill and at the autopsy there was found marked syphilitic leptomeningitis at the base of the brain anteriorly and posteriorly with opaque white areas like small gummata. The left hemisphere was greatly thinned owing to enormous distension of the ventricle. No tubercles could be seen along the vessels. Unfortunately the condition of the blood vessels and of the cerebral tissues was not recorded. Nothing was found in the larynx to account for the spasm and it was concluded that this must have been of central origin

On the other hand the lesions in congenital neurosyphilis may be so localized as to give rise to minimal symptoms, such as isolated pupillary changes or laryngeal manifestations the syphilitic inflammation affecting

presumably only a very small blood vessel supplying a nerve centre or nucleus.

Having treated at some length the causes of the physical manifestations of congenital neurosyphilis, it remains now to speak about the origins of the psychical manifestations of the disease. These may be inherent in the patient from long before birth or they may arise later in a patient who, with an apparently healthy brain, develops normally showing average or even above-average intelligence and ability for a time and as the result of some stress has a mental breakdown in the form of congenital general paresis. This type of case will be considered in a later section. The other type of case, that of original mental defect may be attributable to one or more of the following causes (1) Heredity it was formerly held, though how true it may be to-day one cannot say that acquired syphilis in *an individual usually connoted an inferior mental development or in other* words that the sufferer came from a poor stock. (2) The effect of syphilis in the parents may be to damage the germ plasm to such an extent that the progeny has a bad start. (3) Should this possibility be avoided, the foetus may encounter the third hurdle in subsequent developmental damage to the cerebral tissues due to the treponema or its toxins Sir Frederick Mott (1911) laid great stress upon this point in several of his lectures and publications (4) And lastly postnatal causes of psychical disturbances, as of many of the physical manifestations, may originate in syphilitic meningovascular disease.

The clinical manifestations of congenital neurosyphilis

Reference has already been made to the fact that unless neurosyphilis is actively sought by routine C.S F investigations upon patients, many neurosyphilitics will be overlooked Authorities differ as to when the investigation should be carried out in adults with the acquired disease, whether after 1 year's or after 2 years treatment, but as I have already stated in my opinion in congenital syphilis the C S F investigation should *be carried out as soon as the diagnosis has been made and confirmed* by serological and radiological tests. The C S F may be of Grade 1 or Grade 2 only indicating a slight or mild activity of the meningeal reaction so that although one may say that *active* neurosyphilis is present in the absence of any symptoms the condition would be called *latent* or *silent* It must be pointed out, however that in infants *it is often difficult to be sure* of slight neurological manifestations such as headache slight spasticity pains and so forth On the other hand, the positive C.S F may be associated with convulsions, mental deficiency or paralysis when the condition would be called *clinical* or *manifest* neurosyphilis. It may be mentioned that latent congenital neurosyphilis can occur at any age into adult life and then become manifest or clinical as a congenital G.P I or

tabes. And lastly one has seen patients who were at first sight regarded as latent neurosyphilitics who on closer investigation, have given evidence of disordered personality or of emotional disturbances or other psychopathic tendencies, such as "swearing like a trooper," "fighting wildly on being brought to the clinic," "stealing the toys of playmates in the ward and accusing other children of taking them," and so on.

TABLE 18

925 Patients (mainly Congenital Syphilitics) at Ages, giving the Numbers of Latent and Clinical Neurosyphilis and Non Neurological Cases, with Deaths

Age period	Latent Neurosyphilis			Clinical Neurosyphilis			Non-neurological Cases			Totals		
	Cases	Deaths	%	Cases	Deaths	%	Cases	Deaths	%	Cases	Deaths	%
0– year	36	5	[illegible]	24	(a)	50	331	125 (b)	37·7	391	142	36·3
1 year and over	38	4	10·5	68	24	35·3	428	5 (c)		534	33	6
Totals	74	9	[illegible]	92	36	39	759	130	17	925	175	19

(1) There were 166 neurosyphilitic patients among the 925—just under 18%.
(2) The majority of these patients were congenitally-syphilitic children; the remainder were congenital adults, cases of "possibly-acquired" syphilis and healthy children in syphilitic families.
(a) One additional child died at 13 years from unrelated disease.
(b) Sixteen additional deaths were probably not attributable to syphilis.
(c) Seven additional deaths were not attributable to syphilis, and one death (that of a congenitally-syphilitic mother who died at 48 with heart, kidney and liver involvement) might have been due to congenital syphilis.
In all the patients mentioned in (a), (b) and (c) the W.R. of the blood had become negative.

Table 18 gives details of the neurosyphilis and non neurological cases in our series. The two most important observations brought out by this table are (1) in the under 1 age-group the prognosis of congenital syphilis was almost as serious in the non-neurological cases as in those with latent neurosyphilis, but considerably better than with clinical neurosyphilis and (2) that in the over 1 age-group the mortality rate was very low even before the advent of penicillin. Lastly reference may again be made to our observation that in the over 1 age group clinical neurosyphilis often showed manifestations of parenchymatous neurosyphilis such as general paralysis, tabes and tabo-paresis, mental deficiency and the results of meningovascular lesions, the majority of which failed to respond to the treatment formerly employed. It may be mentioned that Ravaut was for many years interested in latent neurosyphilis: he published a monograph in 1934, wherein he stressed the importance, repeated by Garcia (1953), of studying the cells of spinal fluid during staining with pyronin methyl green (Unna Pappenheim's stain).

Clinical neuro-syphilis symptomatology

In congenital neurosyphilis all kinds of symptom complexes, physical and psychical may be encountered according to the location and duration of the disease. The nature of the lesion will depend upon whether it was inflammatory or meningovascular in origin, and the ultimate result will be

degenerative from softening or sclerotic from scarring On the physical side the effects may be seen in connection with the motor or sensory mechanisms or of both. The former would include fits, seizures and faints paresis or paralysis affecting one or more of the limbs tremors of the face, hands or tongue. In the eyes especially pupillary changes—fixed pupils, unequal pupils, disorders of reaction to light and accommodation facial and other cranial nerve palsies and disorders of speech. On the sensory side there may be anaesthesiae and paraesthesiae, diminished or absent tendon jerks optic neuritis and optic atrophy primary and secondary affections of hearing either acuity or a dulling of the sense of hearing hallucinations, illusions or delusions in connection with the special senses. Lightning pains and gastric crises, ataxia, Romberg's sign and disorders of gait trophic lesions such as perforating ulcers and Charcot's joints On the psychical side all kinds and degrees of mental deficiency antisocial conduct, disorders of personality and behaviour may be encountered Not without due cause has syphilis been called the great mimicker of diseases!

(1) **Syphilitic meningitis** That syphilitic meningitis occurs in many early cases of congenital syphilis, particularly during the exanthem stage is shown by the presence of increased protein and cells in the C.S F the latter practically all lymphocytes with the occasional admixture of a few polymorphonuclears and plasma cells Authors have reported the finding of the causal organism in the C.S F sediment but this is by no means so frequent an occurrence as in the African sleeping sickness, where the *Trypanosoma gambiense* was found in every case of the disease in which it was looked for (Bruce and Nabarro 1903)

Usually syphilitic meningitis is latent or chronic, though it may occasionally pursue an acute course and carry off a patient almost as quickly as may an attack of septic or tuberculous meningitis. We have encountered a few such cases, but as a rule closer investigation revealed a varying degree of local vascular disease in association with the meningitis, together with underlying parenchymatous changes in the grey matter On the other hand, we have seen a case of meningitis (or meningovascular encephalitis) which judging by the result of the C S F investigation (Table 17 case 5) appeared to be acute and severe clear up in the space of 3 months by injections of bisoxyl alone

A history of early meningitis was given by the mothers in several of our patients and mothers frequently stated that they had lost children from early meningitis. Ferguson and Critchley (1929) mention that chronic meningeal inflammatory lesions may be found at post mortem in the absence of corresponding clinical manifestations our experience was unable to confirm their findings and in any event it would be extremely difficult in such cases to be sure that patients had not at some time during their lives had signs of clinical meningitis

Tuberculous meningitis and congenital syphilis Hochsinger (*op cit.* p 156) states, as we have already mentioned, that "a not inconsiderable number of syphilitic children die of tuberculous basal meningitis." Such has not been our experience, for we had only one infant die from the disease in addition one older child aged 10 years and possibly a third in whom the tubercle bacilli could not be demonstrated in the C.S F sediment or clot, although the other changes found in the fluid were compatible with either syphilis or tubercle, died from meningitis. The presence of a positive W.R. in the spinal fluid from a case of acute meningitis does not necessarily mean that the meningitis is syphilitic, in addition to being of tuberculous or other bacterial origin. It is quite possible that an acute meningitis may increase the permeability of the choroid plexus and so allow fibrinogen and the reagin upon which the W R. depends to pass through into the C.S F It will be of interest to give our 3 cases in some detail as each one contributes something to our knowledge of the subject.

Kathleen L., born 1927 was breast-fed for 5 months, had slight snuffles at 6 months and was brought to Great Ormond Street at the age of 7 months to Dr Wyllie's clinic. *The mother then complained of "lateral nodding of the child's head* and a curious movement of the right arm and hand, and it was noticed that the child had a depressed nasal bridge. A few days after admission she developed a vacant look. The blood of both mother and child was tested and found to give strongly positive Wassermann reactions. The diagnosis lay between syphilitic and tuberculous meningitis. In the ward the child showed no squint, the pupils were equal, there was no Kernig's sign and the fundi showed no choroidal tubercles and no choroiditis. Lumbar puncture furnished a C.S.F slightly turbid with a cobweb clot, protein 0·33 % sugar absent, cells 60 to 70 per c.mm. mainly mononuclears, chlorides 5·9 G per litre, Lange 2334431000, W R. strongly positive (4 × 4) and tubercle bacilli present in the stained sediment. The fluid therefore had all the characteristics of a tuberculous meningitis fluid and in addition the strongly positive W R. It is a little difficult to say whether there was also a syphilitic meningitis present, but there was certainly a tuberculous meningitis. In all probability the fluid was not syphilitic and the positive W R. was due to permeation. The father had a negative W R. and had had tubercle, for which artificial pneumothorax had been performed. He gave no history of V D

At post-mortem there were tuberculous changes in the lungs, with giant cells, etc. There were also miliary tubercles in the liver and spleen and typical tuberculous changes at the base of the brain Unfortunately no mention is made in the post-mortem records of the condition of the cerebral and meningeal vessels as to whether they showed any syphilitic changes.

Thomas M., born 1914, was admitted to Great Ormond Street in 1925 with a history of injury to his ankle 6 weeks before admission. Four weeks later he developed pains in the head, drowsiness and loss of appetite. A few days afterwards he vomited after each meal and rapidly wasted. Pus from the ankle joint contained *B faecalis alkaligenes* and no tubercle bacilli His blood and spinal fluid were examined shortly after admission. The blood gave a strongly positive W R. and the spinal fluid gave the following result clear fluid, protein

0·06% sugar slight, cells 15 per c.mm., mononuclears and polymorphs in about equal numbers, trace of globulin, colloidal gold 1122110000 culture sterile. The W.R. was strongly positive. The child rapidly deteriorated and died 10 days after the lumbar puncture was performed. At post mortem there were miliary tubercles in the meninges, the ventricles were dilated and there were numerous tuberculomas the size of a pea in various parts of the brain. The lungs were studded with miliary tubercles. There was a large caseous gland at the bifurcation of the trachea and there were tubercles in the liver spleen and kidneys.

This spinal fluid differs in many respects from that found in the previous case, the infantile form of tuberculous meningitis. The protein is much lower cells are far fewer, Lange weaker and so on, so that one might be tempted to ask whether in the form of tuberculous meningitis which occurs in older children, and especially in the presence of tuberculomas in the brain, the signs of acute meningitis (cells, protein, etc.) may be less marked than in the infantile form. With regard to the W.R. in the C.S.F. we are here confronted with the same question as in the previous case whether this could have been partly syphilitic and partly a tuberculous meningitis or whether the positive W.R. was the result of permeation of reagin from the blood.

The third case is of interest because we had no evidence that it was a tuberculous meningitis and yet it might possibly have been so

Peter C. born 1928 is said to have snuffled at birth and had a rash at 10 days. When he attended the hospital under Dr Paterson at the age of 3 months his spleen was found to be enlarged and X-ray of the limbs showed no sign of bone disease. The blood W.R. of mother and child was strongly positive and the child was treated first with mercury and a fortnight later with injections of sulphostab. An examination of the spinal fluid gave the following result fluid was slightly turbid with a cobweb clot, cells 135 114 mononuclears and 21 polymorphs, protein 0·2% sugar absent N.A. 2, W.R. strongly positive culture negative no tubercle bacilli could be found in the teased clot. Unfortunately the child died at home 6 days after the second injection of sulphostab which was discovered too late for a post-mortem to be carried out.

Except for the lack of demonstration of tubercle bacilli in the clot, these findings would do perfectly well for those of a tuberculous meningitis fluid, and if this were the case the positive W.R. would again be the result of permeation from the blood.

Finally it may be mentioned that we saw several cases in which a diagnosis of tuberculous meningitis had been made on clinical grounds yet pathologically at post mortem syphilis was demonstrably the cause of the meningitis, the organs and tissues showing no signs whatever of tuberculous infection.

(2) **Hydrocephalus.** A serous meningitis with increased subarachnoid and ventricular fluid is a common lesion in congenital syphilis. This was stressed by Jonathan Hutchinson (1862), but the association of a mild hydrocephalus with congenital syphilis appears to have been overlooked

in this country since Hutchinson's time. Hochsinger laid particular stress upon the importance of hydrocephalus in congenital syphilis and maintained that every case of hydrocephalus in infancy should have blood and C.S F investigation. I have for many years held this view and acted upon it whenever possible.

Syphilitic hydrocephalus is not present at birth but develops gradually from the third to the fifth or sixth month of life and it is as a rule slight to moderate in degree. Only rarely does it give rise to the excessive degree of hydrocephalus—the so-called balloon head which is nearly always of non-syphilitic origin. Syphilitic hydrocephalus usually gives rise to no symptoms, nor indeed to any functional disturbance of the nervous system. On the other hand, it may be associated with convulsions, irritability night terrors, sleeplessness and headaches. Ibrahim states that in rare cases of hydrocephalus syphilis is demonstrable only in the mother and that the child's W.R. may be negative. He regards such cases as the expression of a syphilitic dystrophy or parasyphilitic disease. We have encountered this occasionally in our series. Recovery following antisyphilitic therapy and repeated lumbar punctures has been observed, but residual symptoms may persist either in the form of motor disturbances or varying degrees of impairment of the intellectual faculties.

Among the 640 patients whose spinal fluids we examined 112 (17 5 per cent) showed some degree of hydrocephalus or enlargement of the head, of whom 40 (36 per cent) had positive spinal fluids when examined For the reason previously given the number of positive fluids should be considerably greater at least another 10 per cent I estimate, since 218 of 503 patients lumbar punctured (Table 13) had received more than 3 months treatment. Mildly hydrocephalic patients whose spinal fluids were examined before or soon after treatment was begun usually had pathological fluids (either a grade 1 with increased protein cells or Lange curve, or one or more of these abnormalities together with a positive W R.), which would indicate that the hydrocephalus was a sign of neurosyphilis. On the other hand a big, bossed head with a negative spinal fluid probably indicates a bony rather than a neurological lesion or the hydrocephalus is to be regarded as the only manifestation of an otherwise latent neurosyphilis. If however there were concomitant symptoms of active disease present, such as fits, hemiplegia, blindness, etc. the C.S F would almost certainly be found pathological.

We found many of our hydrocephalus cases interesting and instructive. A few of them are given in detail

The patient (Alfred M) has been referred to on other occasions, but as he was suffering from hydrocephalus and his subsequent history induced me to write on his record card that "*all hydrocephalus cases should have a Wassermann done*" this seems to be an appropriate opportunity to recite his case.

There was a history of syphilis in the father acquired in the first world war

for which he received treatment. The patient was born in 1922, had snuffles but no rash, and at about 3 months of age is said to have had hydrocephalus. He attended one of the smaller children's hospitals in London from the age of 5 months and was given mercury tablets, which he took until he was 2 years old. At $2^{1}/_{12}$ years he developed paralysis of the right arm and leg for which he was sent to a special hospital, where meningitis was diagnosed. At about this time he lost the power of speech and was unable to stand.

He was brought to Great Ormond Street at the age of $2^{5}/_{12}$ years and was seen by a physician who noted that "the head was 20½ in. in circumference and that there was a right-sided hemiplegia." No diagnosis was made, nor was a blood Wassermann or lumbar puncture asked for. The patient was ordered massage to the right arm and leg, and the treatment given was cod-liver oil and malt. Three months later he developed a swelling in the right parotid area and was one of the patients included in the description of parotitis in congenital syphilis (see Chapter 7 p 159). Shortly after this he developed a lesion in the left eye, which Mr Doyne, our ophthalmic surgeon, thought was almost certainly interstitial keratitis. The blood and spinal fluid were now examined at 2¾ years blood was very strongly positive, the C.S.F clear cells 25–30 per c.mm., protein 0·16 Nonne 3 Lange 5554321000, W R. ++++ (Table 17 case 6, p. 279). In September of that year he developed herpes, another interesting lesion which one has found associated with congenital syphilis in a number of cases (see p 294). After 3 courses of sulfarsenol he began to show signs of improvement. He was able to stand alone for a short time and his speech was beginning to return. The eyes at this stage showed some inequality of the pupils, the left being larger than the right, but the fundi were normal.

The C.S.F appeared to indicate a severe infection of the C N.S. of the paretic type the only slightly encouraging manifestation being the paucity of cells present. From this one investigation of the fluid one would be inclined to give rather a bad prognosis to the case but as the patient improved considerably under treatment, and particularly as the next investigation of the fluid 14 months later gave practically a normal result the sinister early prognosis would be considerably modified. After further treatment, this time with bismuth preparations, the serum W R. became gradually weaker but was not finally negative until the patient was 9 years old. His paralysis improved, he was able to walk eventually without an iron, but the right hand was still paralysed. The mother stated that the boy could understand everything that was said to him, but he spoke very little. He was clean in his habits. At the age of 13 he began to have turns. He fell off his chair but did not lose consciousness, and he also had periods when "his hands shook. A final blood and spinal fluid test then taken gave normal results and as the lad was now at an age when he had to leave school, yet had learnt nothing he was transferred to an institution for mental defectives. Upon inquiry one heard recently (1953) from the medical superintendent that the patient was still alive at the age of 31 years. He suffers from epilepsy and has about one attack a month. He is able to walk and is quite a useful worker in the ward. He appears not to have deteriorated, physically or mentally since he was admitted in August 1938."

This is a remarkable but at the same time a tragic record remarkable because from the first C S F result one would have thought that the patient would have died from G P I within a few years and tragic because having survived for so long it will be necessary for him to remain under institutional control for the rest of his life Probably had lumbar puncture been

carried out earlier when he first came under observation with his hydrocephalus, the neurosyphilis might have been rapidly cured and the subsequent damage to his brain averted by appropriate treatment.

Valerie W., born June 1920—half a twin—the brother being also positive. Both children had a rash at 3 months. The boy when seen at the age of 14 months was a case of latent congenital syphilis. The girl had hydrocephalus in infancy and when seen at 16 months the head was enlarged, but there was no craniotabes. The C.S.F. was clear no clot protein 0·05% cells 65 per c.mm. mainly small lymphocytes, N.A. negative, Wassermann 4-4-4-4. When readmitted the following August (1921) the condition had very considerably deteriorated and the child died a fortnight later The C.S.F. result was similar to the



FIG. 85 Photograph of a child aged 8 months with syphilitic meningitis and a fair degree of hydrocephalus. Note the turgidity of the veins on the forehead

former except that fewer cells seemed to be present (20 to 25). At the post mortem many adhesions were found between the meninges and skull and the vessels were thickened (see Table 17 case 2, p 279).

Louisa W., born October 1924. Patient snuffled a little in infancy and is said to have been an in-patient for a fortnight at another hospital from which she was discharged as "being well. On admission to Great Ormond Street at the age of 8 months, it was stated that the child had never been healthy There was a mild degree of hydrocephalus present (circumference of head 16½ in.=41·2 cm. see Fig 85 and there was no protrusion of the eyeballs. An X-ray of the skull showed a widely open fontanelle and thin cranial bones. An X-ray of the limbs showed no signs of periostitis. Lumbar puncture furnished a slightly turbid fluid of a paretic type (Table 17 case 3). Although the W R. of the fluid was strongly positive that of the blood was negative, which is the only instance of this combination I have met with in an untreated congenital syphilis patient. Death occurred a few days after admission. At the post mortem there was very marked hydrocephalus with adhesions of the meninges at the base of the brain between the medulla and the cerebellum There was marked granularity of the ependyma of the ventricles as in G.P.I

The cerebral vessels and sinuses appeared healthy. Except for slightly increased fibrosis there was not much change to be detected in the abdominal viscera.

The two points of interest in the case were (1) that although the child was obviously a congenital syphilitic her blood was negative and the spinal fluid positive; (2) the other was the family history, for the mother was herself a congenital syphilitic, having attended Moorfields Eye Hospital at the age of 7 to 8 years for interstitial keratitis, and her blood was very strongly positive when examined in 1925. She then had 3 children, of whom the patient was the second. The first and third both appeared to be healthy and had negative blood tests (see Chapter 9, Third-Generation Syphilis).

Leslie D., born 1924, had no infantile symptoms of syphilis and was brought to Great Ormond Street at the age of 8 months, when he was "very small and had hydrocephalus, with the left side of the head more prominent than the right posteriorly." His blood and spinal fluid were both found to be strongly positive (see Table 16, case 7). *He* was treated intensively with sulfarsenol and bismuth, but unfortunately as he lived a considerable distance from the hospital his mother defaulted several times, in spite of our warnings. As a result the spinal fluid and blood remained strongly positive for 5 years despite the treatment he received, which included tryparsamide. Ultimately he was given malaria, during which his temperature rose on two occasions to 106·8° F so that after 6 paroxysms it was thought advisable to stop the attacks. It is of interest to note that after the malarial attacks, the liver and spleen had become much enlarged, the left lobe of the liver reaching down to 4 fingers' breadth below the ensiform, and the edge of the spleen 2 fingers' breadth below the costal margin. Tryparsamide injections were continued, with the result that 2 years after the malaria was given both the blood and C.S.F. had become negative. The child was subsequently given stovarsol (about 4½ G. in all) and the blood and spinal fluid remained negative, the former to the age of 12, and the latter to the age of 10, when they were last tested.

Among earlier notes of progress it says: "At 18 months the child has improved, the head is much smaller and better-shaped than when he first came under observation." At 3½ years it was noted that he was still very small in size. At 5 years of age there was nothing abnormal to be seen in his fundi, but at 5½ he started watering of the right eye, probably due to a blocked duct. The C.S.F., which was strongly positive at 8 months, became negative at 7 1/12 years, although it is possible that it may have been negative before this and slightly before the blood. We have also a note saying that the child was bad-tempered; this is an observation I have made in several cases of neurosyphilis, though perhaps in view of the enormous amount of treatment this patient had undergone, involving innumerable prickings, it is not to be wondered at that his temper was somewhat frayed.

Constance S., born March 1929, had hydrocephalus, slight depression of the bridge of the nose and overhanging forehead (Fig. 86). She was brought to the hospital at the age of 3 months on account of progressive enlargement of the head and spasm of the legs. X rays showed typical epiphysitis at the lower end of the humeri and the child was very anaemic (R.B.C. 1·5 million, W.B.C. – 500 per c.mm., Hb 30%), for which she was given a transfusion of 110 ml. of the father's blood. The C.S.F. gave the following result: very slight opalescence, protein 0·1 %, cells 27 per c.mm., slight reduction of Fehling, chlorides 6·3 G. p.l., Lange and N.A. trace, W.R. 4400. Patient died very shortly after

admission and at post-mortem the brain was found to be very soft, with much gelatinous exudate all over vertex and base. The lateral ventricles were very distended.

Peter W., born Sept. 1924, began to suffer from enlargement of the head at the age of 3 months and on admission to the Children's Hospital under Sir Lancelot (then Mr.) Barrington Ward the forehead was noticed to be broad and square. Neither the C.S.F. nor the W.R. of the blood was examined during life but post mortem the spinal fluid gave a strongly positive W.R. and both



FIG. 86. Moderate degree of hydrocephalus in a syphilitic infant aged 3 months. The forehead was overhanging and the scalp vessels prominent.

At post-mortem, basal and vertical meningitis was present: the brain very soft and the lateral ventricles much distended. Treponemata were found in the cerebral cortex.

parents were found to give a positive blood test. At autopsy there was a large external hydrocephalus, mainly on the right side, with fluid and gelatinous material between layers of false membrane. There was also a left empyema, the "pus" being very green and consisting of a gelatinous lymph showing many pneumococci. The lungs were rather fibrotic.

Derek C., born Oct. 1929, had snuffles and a rash all over the body at the age of 3 weeks. His head began to enlarge at 3½ months, and at 5 months when he came under the care of Dr. Bernard Schlesinger at the Hospital for Sick Children papilloedema was present. The cerebrospinal fluid was normal in all respects,

including a negative W R. The blood gave a positive W R., as also did the mother's blood. On examining the mother more closely her upper central incisor teeth were seen to be barrel-shaped and suggestive of congenital syphilis (see Fig 39). This suspicion was strengthened by eliciting the fact that the mother's sister had suffered from eye trouble for which she received injection treatment and that a brother had "hydrocephalus and leg trouble." An X ray of the infant's limbs showed no abnormality but on account of the history of *rash and snuffles and the positive blood test arsenical injections were given.* The head continued to enlarge, however reaching a circumference of 19½ in. (48·8 cm.), so that surgical intervention was decided upon. First one then the other internal carotid artery was tied, but the child died after the second operation. Cisternal fluid obtained after death showed somewhat increased protein (0·04%) and cells (36 per c.mm.) but again a negative W R. Unfortunately an autopsy was refused.

The family history was interesting The mother was a latent congenital syphilitic, a sister and probably also a brother suffering from the disease. The *mother's and child's blood both gave a positive W R.* but the *husband's blood* was negative. There were 2 older children who were said to be well and there had been no miscarriages. We could not induce the mother to bring the 2 older children to the Clinic for investigation.

(3) **Cerebral vascular lesions.** In the chapter dealing with the cardiovascular lesions in congenital syphilis reference was made to the frequency with which the medium sized and smaller cerebral vessels were affected This commonly occurs in infancy usually from the age of 9 to 18 or 24 months in the form of a panarteritis (end mes and peri arteritis), which often results in thrombosis within the vessel or vessels involved (Fig. 84). The clinical manifestation of this, as we shall presently see is a true paralysis as opposed to the pseudo-paralysis of Parrot which usually occurs at an earlier age. This type of vascular lesion is rarely if ever seen apart from meningitis, so that it is customary to regard cerebral syphilis in the infant as being primarily meningovascular in nature and origin. *The spread of the syphilitic process to the subjacent grey matter* may convert the condition into a meningovascular myelitis or encephalitis. In older congenital syphilitics changes indistinguishable from atheroma arteriosclerosis and aneurysm have been described especially in cases of congenital general paralysis.

(4) **Paralyses of the extremities.** Paralyses may occur in syphilitic infants *almost from birth onwards. We have seen that syphilis is prone* to give rise to haemorrhage in the newborn, so that some of the birth injuries which eventuate in an early infantile paralysis and are diagnosed as Erb's paralysis and Little's disease may be produced in this way A commoner causation as stated in the previous section is thrombosis resulting from cerebral meningovascular disease, which usually gives rise to a hemiplegia, but sometimes to a monoplegia or paraplegia (Fig 8). It was my experience with several of such patients that the syphilitic disease underlying their clinical condition was not recognized or even suspected by the physician or surgeon in charge with the result that the medical

treatment the patients received while being harmless, was useless from a curative point of view Meanwhile, in default of antisyphilitic treatment the various surgical operations on muscles, nerves and tendons were usually accompanied by concomitant mental deterioration, which



FIG 87 Spastic diplegia (with right hemiplegia) of syphilitic origin in a girl of 8½ years—originally diagnosed at 2½ years as meningitis and treated with penicillin.

This unfortunate patient should not have been allowed to reach the age of 5 years before being diagnosed as syphilitic. At 2½ years the nature of the meningitis should have been ascertained and prompt antisyphilitic measures taken. Really the child *should not have been born syphilitic had adequate* precautions been taken during pregnancy

sometimes progressed to a condition of general paralysis. In order to clinch the diagnosis of neurosyphilis it is essential that the C S F be investigated as well as the blood Wassermann reaction for a positive serum W R. would not be conclusive evidence, in the absence of pathological changes in the C S F that the nerve lesion was of a syphilitic

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not specified. Of the 13 cases no fewer than 10 occurred in patients with congenital neurosyphilis, but in 3 of these the spinal fluid examination gave a negative W R. when examined at the ages of 4½ (twice) and 8⁴/₁₂ years respectively after treatment had been given so that the fluid might possibly have been positive had it been examined earlier From these figures it would certainly seem possible that syphilis, and particularly neurosyphilis, may open the way to infection with the virus or viruses of herpes. The patient with ophthalmic herpes was a girl aged 12¾ years at the time, a neurosyphilitic who suffered from dispituitarism. The herpes affected the right eye only the eyelids being oedematous and closed. Our ophthalmic surgeon, Mr Doyne, reporting on the case, wrote She seems to have a very atypical *herpes ophthalmicus* possibly due to a direct involvement of the Gasserian ganglion in the syphilitic process." The first case was observed in 1920 in a patient aged 2⁷/₁₂ years and the last one in 1936 in a patient aged 6 years who developed sciatic herpes all down the leg after intensive treatment with tryparsamide and bismuth and several courses of sulphostab injections. The C.S F was positive for 2¾ years after discovery but it had become negative when the herpes appeared

(*b*) *Syphilis and poliomyelitis and encephalitis* We have records of 17 patients in whom there appeared to be some association between these conditions, syphilis and virus myelitis or encephalitis, and they can be divided into three categories (1) 7 cases of congenital neurosyphilis which were diagnosed, I believe erroneously as polio-encephalitis, poliomyelitis or encephalitis lethargica or vaguely as encephalitis without assigning any aetiology (2) 5 cases which were diagnosed as poliomyelitis or ? poliomyelitis in congenital syphilitic patients, one or more of which may have been instances of neurosyphilis and (3) 5 cases diagnosed as poliomyelitis occurring during the treatment of congenital syphilis. A few illustrative cases from these three groups may be of interest

Group 1

Norma S., born 1932, was admitted to Great Ormond Street at the age of 11 months with the following history She snuffled at the age of 3 weeks and after attendance for some weeks at another children s hospital syphilis was diagnosed at the age of 9 weeks and appropriate, though somewhat inadequate, treatment was given. The infant seemed to be making good progress when, at the age of 1 year and after the child had learnt to stand, she had a sudden hemiplegia which was *unaccompanied by any previous febrile attack*. On examination the left arm was found to be weak, as was also the left shoulder and leg The knee jerks were increased and the triceps jerks were present. There was a spastic condition of the left arm, with spasm of the fingers of the left hand. The blood and C.S.F both showed a positive W R. and the latter in addition contained 100 cells per c.mm., all mononuclears, protein 0·05° and weak Nonne and Lange reactions. The physician in charge of the patient thought it was a case of poliomyelitis, but two neurologists who were asked for their opinions agreed with the writer that the condition was due to congenital neurosyphilis and probably the result of a cortical lesion following upon a lesion of the

middle cerebral artery rather than to poliomyelitis. The spastic condition of the arm, the state of the reflexes and that the cells in the C.S.F were all mononuclears were considered to be evidence against the diagnosis of poliomyelitis. The child was accordingly treated with sulphostab combined with pills of mercury iodide, and after only 3 weeks treatment power was beginning to return to the left arm and leg At the end of 3 months the child's condition had much improved and 7 months from the onset of the trouble she had again started to walk. At this time (18 months) the C.S F had become normal in all respects and the serum W R. had also become negative. Antisyphilitic treatment was continued until the patient was 3 years old, but from the age of 2 years she was walking well and could use her left arm and leg normally Unfortunately she was lost sight of at the age of 4½ years in 1937

The family history was interesting The child's father gave no history of syphilis or of any venereal infection and his W R. and Kahn were quite negative. The mother on the other hand, was said to have a strongly positive W R. at another hospital where she was thought to be suffering from congenital syphilis with signs and symptoms of congenital tabes dorsalis. She was given treatment at that hospital and in 1933 her W R. and Kahn were said to be still strongly positive. Her first pregnancy which occurred soon after marriage resulted in a full term stillbirth and our patient was her first living child.

James K. born May 1932 was a small baby at birth had no snuffles or epiphysitis but a rash at 8 weeks which the G.P diagnosed as "impetigo" He is said never to have been well to have started convulsions at 8 months and to have had hemiplegia at 10 months. On admission to hospital there was marked rigidity of the whole body the right arm was useless, knee jerks were obtained with difficulty and the plantar reflexes were flexor The C.S F was very slightly turbid and contained 60–70 cells, all lymphocytes, protein 0·16* there was good reduction of Fehling Nonne 2 Lange weak luetic curve W R. strongly positive. Serum W R. was also strongly positive. The physician in charge diagnosed the case as being one of tuberculous meningitis, but there was no evidence of tubercle present at the post mortem which was carried out two or three days later On the other hand there was very definite syphilitic disease of the cerebral vessels and meninges, and the internal carotid and middle cerebral arteries were almost occluded by syphilitic arterial disease (Fig 83). Sections of the brain showed thickening of the pia-arachnoid with perivascular cellular infiltration the infiltration spreading also into the cerebral parenchyma. The brain tissues, especially in the left cerebral hemisphere, were almost necrotic No definite treponemata could be seen by Jahnel s stain.

Lilian C., born 1924, had weakness of the right arm and leg at about 4 months which was ushered in by a succession of fits. She was brought to Great Ormond Street when about 8 months old when the head was found to be enlarged weakness of the right arm and leg was present and the child was thought to be blind The clinical diagnosis made was encephalitis, which was no doubt literally correct, but on repeating the lumbar puncture the following week when a W R was carried out upon the fluid the W R. was found to be strongly positive and the encephalitis was shown to be syphilitic in nature

The following case which was diagnosed as encephalitis lethargica is of considerable interest. It occurred during the late war when a soldier was admitted to the Blind School Hospital at Leatherhead with the diagnosis of

encephalitis lethargica. On examining the patient his rather suggestive teeth made one think he might be a case of juvenile G.P.I., and blood and spinal fluid investigations confirmed the diagnosis. He was one of several cases of this kind which one had encountered—children of soldiers in the first world war who were born after the father had contracted syphilis for which he had received a certain amount of treatment but not sufficient to effect a cure. The congenital syphilis which the child inherits is of so mild a nature that in such a case it is not diagnosed, and possibly even not diagnosable, but the patient tends to break down under the stress of some mental strain, in this case the excessive training which recruits had to undergo at that time. The patient was removed to a military hospital and his further history is unknown. Since reporting this case one has been informed of several similar instances (see also p. 406).

Group 2

Ronald K., born 1930, was the brother of James K., mentioned in Group 1. He was small at birth, had no snuffles or epiphysitis, but at 7 weeks had a rash which the G.P. diagnosed as "impetigo," just as he did in the case of the younger brother. At the age of 16 months he developed a hemiplegia of the right arm and leg, for which he was brought to Great Ormond Street Hospital and the condition was diagnosed as acute encephalitis. Three days after admission to the ward he developed a right facial palsy without there having been any antecedent feverish attack. Knee and arm jerks and abdominal reflexes were present; the right plantar reflex was extensor. The C.S.F. was clear: cells 370 per c.mm. (88% lymphocytes, 12% polymorphs) protein 0·035%. The Nonne, Lange and W.R. not having been asked for by the clinician, were unfortunately not examined on this occasion. The fluid would have been compatible with either a polio or with neurosyphilis, but in the absence of the Lange and W.R. one cannot say with certainty. At the age of 3 years he was brought again to the hospital in order to undergo an operation for lengthening the tendo Achillis, and it happened at the same time his brother James was in another ward and was found to have a strongly positive W.R. This led to the investigation of this child's blood and spinal fluid, with the result that the W.R. was found to be strongly positive in both fluids and there were other signs of neurosyphilis (protein 0·04%, cells 21, Nonne 1, Lange 2333210000) in the C.S.F. It is therefore probable that neurosyphilis was the cause of his hemiplegia and right facial palsy which occurred 2 years previously.

John P., born June 1931, suffered from snuffles at the age of a fortnight, but had no rash or clinical epiphysitis. An X-ray at 4 months of age showed the presence of periostitis of the long bones and his serum W.R. was strongly positive. The C.S.F. taken at 5 months was normal in all respects. Shortly before he was 2 years old the child began "to drag the left leg," which Dr. Wyllie, the physician who saw him, originally thought might be poliomyelitis. This condition persisted for a considerable time, and the patient was seen also by Mr. Eric Lloyd, our orthopaedic surgeon, who concurred in the diagnosis. The left leg subsequently became wasted and was smaller and colder than the right and eventually Wyllie came to the conclusion that the condition was the result of some congenital abnormality.

Group 3

The cases of polio occurring during treatment of congenital syphilis. These cases did undoubtedly occur and they might have been due to a virus, as has been recorded now for some years in virus hepatitis and jaundice.

In our clinic we always sterilized our syringes by boiling and thoroughly rinsing them out in fresh sterile water between the injections of patients Admittedly the same syringes served also for taking blood from children for Wassermann tests We very rarely came across a case of jaundice, so there could have been no cases of obvious hepatitis, but possibly the nerve type of virus may have been so conveyed as so many of the cases were neurosyphilitic. It appeared to me that the average non-neurological physician was apt to diagnose acute anterior poliomyelitis or acute encephalitis too lightheartedly and on insufficient grounds and bearing in mind the disastrous consequences, physical, psychical and surgical to the unfortunate patients, it cannot be too strongly urged that in *all* cases of hemiplegia or paralysis in young children a blood W R. and C S F investigation, including W R. should be carried out before the vague and noncommittal diagnosis of hemiplegia, encephalitis, anterior poliomyelitis, Little s disease, cerebral or spastic diplegia, etc. is made.

In addition to the 17 cases recorded in the above three groups in which there appeared to be some association between syphilis and poliomyelitis or polio-encephalitis, there were 14 others, making 31 cases in all, in which paralysis of the extremities was present In 27 of the patients syphilis was diagnosed by the finding of a positive W R. in the blood and/or C S F In the remaining 4 the child s W R. was negative but a syphilitic aetiology was probable since either or both parents were definitely syphilitic. In a few of the cases there had been a history of a fall on the head before the onset of the paralysis which may have been the exciting cause of the lesion inasmuch as the blood vessels of a syphilitic child are more liable to rupture than those of a healthy child.

(c) The *parotitis* cases referred to in Chapter 7 may be further examples of the association of viral diseases with syphilis.

(5) **Convulsions and fits.** *It is not uncommon to get a history of con* vulsions (seizures, turns, fits, etc.) in congenitally syphilitic children and it is at times difficult to determine whether these are of a syphilitic nature or whether they are due to banal causes. They are often diagnosed as being epileptic, so that the problem of convulsions, seizures and epilepti form attacks in a congenitally-syphilitic individual is a difficult one to adjudicate upon and indeed divergent views have been held by different observers. In this country Gowers and Turner have held that congenital syphilis plays *only a very small part in the aetiology of epilepsy* On the other hand Mott was of the opinion that congenitally-syphilitic patients were liable to many neurological disorders—G P I tabes, tabo-paresis, primary optic atrophy chorea, hysteria, meningitis and epilepsy French writers have long held the view that parental syphilis plays an important part in the aetiology of epilepsy in the offspring Bratz found evidence of inherited syphilis in 5 per cent of epileptic patients, and Jeans and Cooke say that they are convinced that syphilis is a cause of epilepsy

Our own experience has been that fits may occur in quite young syphilitic children, in which case they may frequently be associated with an acute, subacute or chronic meningitis. On the other hand fits may occur rather later in infancy from the end of the first year in association with meningovascular disease, when they may be the precursors of a more serious parenchymatous disease of the brain. Frequently a fit may be followed by loss of power in one or more of the limbs, so that the hemiplegia, which is rather a common feature of congenital neurosyphilis, may start with a convulsion. Having once started in this way other fits may occur fairly frequently and at irregular intervals, or they may remain in abeyance for months, sometimes even for years, before the patient is again attacked. In nearly all these cases the C.S F is pathological. As the result of energetic treatment the fits may be reduced in number but at times the intervals between them become shorter and shorter and occasionally the patient may die in a condition of status epilepticus. On the other hand, the more common event is for the patient to develop symptoms of general paralysis, during the course of which a variable incidence of convulsions or seizures may occur This is so commonly the case that in the death certificates of these patients epilepsy has practically always figured among the causes of death and in most cases congenital syphilis has been omitted. We had several patients who were clinically considered to be epileptic, with negative blood and C.S F yet were of syphilitic parentage. It is impossible to say whether parental syphilis had been the actual cause of the epilepsy in the child, but the fact remains that these two conditions, syphilis and epilepsy have been present in parent and child respectively This association of parental syphilis and filial epilepsy is referred to by Collin in his book on epilepsy in children. In some of these cases in which the child was not itself a congenital syphilitic, the Wassermann reaction in both blood and C.S F has been negative and one found that the patient did not derive any benefit from antisyphilitic treatment. It was assumed therefore, that in such a case the condition was not truly syphilitic but rather of a para-syphilitic nature. Mott wrote in 1911

If syphilis can produce arrest of the development of the reproductive organs, there is surely no reason why it should not lead to arrest of development of the most highly differentiated and specialized tissues of the body namely the cerebral cortex, or cause pathological variations in its structure and function. If this view is correct, which I believe to be the case, it follows that injury to the germ-plasm may be the cause of many defects of the nervous system resulting in mental retardation and a predisposition to epilepsy and various psychiatric disorders.

In several of these cases of paralysis of the extremities mental deficiency may coexist. Not infrequently the paralysis has been heralded by a fit and occasionally a transient aphasia has been noted In the large majority of these cases of paralysis we have found the outcome extremely

unsatisfactory for even should one succeed in curing the patient's syphilis and in rendering the neurosyphilis inactive *as evidenced perhaps by a* negative serum W R. and a normal C S F the associated mental defect tends to be progressive and to lead to the patient's death either in the first few years of life or at any subsequent age up to 20 or 25 years

In addition to the cases of paralysis which were due to the syphilis *itself* we came across 4 cases of paralysis and encephalitis which were the result of arsenical treatment and which will be referred to more in detail under that heading

(6) **Cranial nerve palsies.** The cranial nerves may be affected (1) by the syphilitic toxin acting upon their nuclei in the brain, or (2) anatomically at their exit from the brain or along their course by syphilitic meningitis, or more rarely by gummata (Barlow and others) or (3) by disturbances of their nutrition occasioned by syphilitic disease of their blood vessels The oculomotor and facial nerves are most frequently affected so that irregular or fixed pupils, some form of squint or facial palsy may be among the *resulting manifestations of the condition.* (*I should like to emphasize* here the importance of noting the presence of unequal and/or fixed pupils *because, although* not pathognomonic of congenital syphilis, fixed or unequal pupils should arouse one's suspicion of the possibility of the disease, and if a blood test should confirm the suspicion, the C.S F should be investigated because of the probability of neurosyphilis being also *present.*)

We had a *few* cases of facial palsy in infants and may mention in particular one infant 3 months old who developed a facial palsy a few hours after its second weekly injection of bisoxyl (0·2 ml.). The condition was regarded as being of the nature of a Jarisch-Herxheimer reaction and it disappeared within five days without any special treatment. The C S F investigation showed the presence of neurosyphilis (cells 50 per c.mm protein 0·06 per cent, W R. moderately strong). The weekly injections of bisoxyl (0·3 0 4 ml. etc.) were continued without any subsequent reaction and the fluid became normal after 10 bisoxyl injections.

Optic neuritis has been recorded by several observers in congenital syphilitic infants We have seen 2 cases of the condition and Nonne reported a number of cases, some of which were cured by antisyphilitic treatment. Deafness was formerly regarded as a characteristic symptom of congenital syphilis and formed one of the three components of Hutchinson's triad It is less common in infancy than in later childhood and consequently owing to the better treatment of congenital syphilis, fewer cases are encountered to-day than formerly

Congenital G.P.I

Originally G P I was thought to affect only adults and that it did not *usually occur in patients* under 25 years of age Clouston, in 1877

reported the first case of congenital G.P I in a boy of 16 and 2 years previously *Hughlings Jackson reported a typical case which started at the* age of 15 the lad dying at the age of 17 That case, however was not recognized as being one of general paralysis but was reported under the title Nerve symptoms in congenital syphilis. Since that time so many cases have been recorded—Sir Frederick Mott, for example, having had notes of no fewer than 60 personally observed cases—that the condition is now no longer regarded as a rarity Tennent (1936) states that apparently 1 to 2 per cent of all cases of G.P I are of the congenital (juvenile) variety and Stewart (1933) considered that about 1 per cent of all cases of congenital syphilis develop general paralysis. The age of onset has been gradually lowered, so that cases have been recorded at 6 5 and even 4 years of age.

In considering the age of onset and the types of congenital G.P I., we are confronted with obvious difficulties. By definition the disease implies a progressive mental and physical deterioration due to syphilitic degenerative changes in the cortex of certain areas of the brain, with increased gliosis and concomitant changes. These criteria are difficult to apply to infants and very young children in whom behaviour and mentality changes are impossible to assess and primary mental deficiency due to retarded development may be present. Often also meningovascular disease is present, the progress of which leads to further mental and physical deterioration, often with fits or seizures or oculomotor troubles, etc. The C S F may resemble that in adult G P I (see Table 17), even to a paretic Lange curve, though this may improve under treatment, as we have found in both congenital and adult G.P I At post mortem all varieties of changes may be found basal or vertical meningitis with lymph over the surface or with adhesions of the meninges, dilatation of the ventricles with granular ependyma (2 cases at least) Many of these cases have meningovascular disease, with extension to the surface of the brain giving rise to encephalitis, which is a cause of the increasing dementia so often seen in these patients. It is this type of case which has induced writers to suggest that G P I may date from birth (Menninger 5 out of 40 cases, Stewart 8 out of 14) We have had at least 16 such cases, 12 of them under 1 year of age and 4 in the first few years of life, which all come into this category The 12 under 1 year of age died in infancy of the remaining 4, all with typical paretic fluids, 2 were still alive in 1950 (Table 17 cases 5 and 6) at 19 and 28 years of age respectively The patient M H a girl aged 19 was then mentally and physically backward facile with somewhat defective speech and an external strabismus. She was first seen at the age of 2½ years and there is a history of her having had fits from 7 to 16 years of age.

The other patient still alive (1953) at nearly 31 years of age, Alfred M was referred to under hydrocephalus (p 287) The case was rather

suggestive of G.P I at the first spinal fluid investigation, but at the second investigation 16 months later the fluid had become practically normal, so that the prognosis was considered to be more favourable than it was originally In spite of having an occasional fit, the patient is apparently able to do useful work in the institution of which he is an inmate and he can hardly be regarded as a typical case of G P I

Of the remaining two one developed a paretic type of C.S F at 7 years of age after 2 years mercury treatment and a default of 5 years. He was then treated with sulfosin, malaria and intracisternal injections of salvar sanized serum. He died at the age of 12 years of septic meningitis secondary to otitis media (this may have been syphilitic) The other (G J Table 17 case 4) had a negative W R. at 5 years after the blood had relapsed twice, and his paretic spinal fluid had also become negative at that age. He survived until he was 17 having suffered from fits the whole time.

The *second type* of congenital G P I which is the one more generally recognized by paediatricians, neurologists and psychiatrists, is that in which the patient has apparently been developing normally showing average or even above average ability at school and sometimes even having been regarded as precocious, when sometimes abruptly but more usually gradually he begins to show evidence of mental deterioration

The *third type* of case is that which occurs in adolescents or young adults and partakes of the nature of acquired G.P I in its symptomatology and course. This type of case may occur in individuals who are not known to be congenital syphilitics and who under some stress may break down mentally in the form of G.P I., but which, as in the case of the patient mentioned on p 296 was thought to be clinically a case of encephalitis lethargica. It is important to bear in mind that this type of G P I may occur as late as the third or fourth decade of life and therefore may be looked upon as an acquired case of G P I if the history is not carefully inquired into (case of Mrs. A p 306). The relative number of cases occurring in each group will depend to a considerable extent upon the type of practice followed by the physician recording the observations, whether paediatrician neurologist or neuro-psychiatrist. This is well brought out by the differences recorded in the ages of onset. In Mott's first series the average age was 17 years in Ferguson and Critchley's 16 cases the average age of onset was 13 years Stewart as already men tioned had 8 cases in infancy and 6 in the older age-group

Of our own 20 cases of undoubted and possible G P I patients (Table 19) in addition to those already mentioned as occurring in infancy and the first few years of life, the average age of onset was 11 3 years the youngest being 4 and 5 years of age and only 3 of the patients being over 20 namely 23 28 and 36 In type 3 there is as a rule little difficulty about the diagnosis but in type 2 one may come across difficult cases

which some authorities might call G.P I and others might regard as cerebral syphilis with secondary dementia. This in the long run makes very little difference to the patient, although possibly cerebral syphilis may be rather the more amenable to treatment.

In the congenital form of the disease the sexes are said to be affected equally in contrast to the higher ratio of males to females in the acquired form, but our 20 cases showed 12 males to 8 females

The clinical course of the congenital disease is longer than that of the acquired, but since the introduction of malaria and penicillin in treatment this is probably no longer the case. Certainly it appears that patients in whom epileptic attacks and convulsions are frequent succumb more rapidly than those not so affected. The stigmata of congenital syphilis may be present in possibly a third of the cases which develop G.P I and it is frequently found that these patients are undersized and sexually under developed and may show evidence of other endocrine dysfunction Our cases had an average duration of 6½ years, but 3 out of 20 have so far survived and are of particular interest.

Ellen K. started at the age of 6 and as an account of her case is given in the *Lancet* (1927) it will be necessary to give only a résumé of the case here. The child was admitted to Great Ormond Street under Dr (now Sir) Robert Hutchison, suffering from mental disorder" The history stated that the onset was sudden and it was on that account that it was considered to be an ideal case to test the latest methods of treatment, as presumably being so abrupt in its onset very little damage would have been done to the C.N.S. and the outlook would be correspondingly promising Upon inquiry however it was ascertained from the schoolmistress that she had noted the child s peculiar behaviour during the previous 5 months, so that it was obvious that the onset was not so sudden as the parents had led us to believe. There was no history of syphilis in the family but there had been one miscarriage at 3 months before the birth of our patient. On admission, the patient was physically well-nourished and healthy-looking, but was quiet and sullen, and appeared to be unable to understand what was said to her She was dirty in her habits, noisy and destructive her speech was indistinguishable and on account of her mental condition physical examination was difficult to carry out. The heart and lungs appeared normal, but it was impossible to make an adequate examination of her C.N.S as she was so resistant and demented. Vision appeared to be normal and the pupils reacted to light and accommodation. There was no nystagmus. Knee jerks and abdominal reflexes were increased and the plantar reflexes were flexor Under an anaesthetic the eyes showed typical choroido-retinitis. At times she would smile fatuously and at other times made meaningless noises she had many fits of crying and turned away from anyone near her She resisted all examination. She appeared to be suffering from headaches, as she frequently put her hands to her head and screamed. An examination of the blood and C S F confirmed the diagnosis of congenital G.P I Dr Hutchison having kindly transferred the patient to my special V D ward for treatment I gave her two courses of intracisternal injections of salvarsanized serum which had been demonstrated to me by Sir James Purves-Stewart. This resulted in a very considerable improvement in the C.S F but not in a parallel improvement in the child s mental condition. Accordingly she was given a course of malaria

TABLE 19

The First C.S.F. Investigations in 20 Cases of Congenital (Juvenile) G.P.I. or Allied Conditions

	Date of birth	Clear	Cell	Protein	Sug	[illegible]	Lange	W. R.	S. W. R.	Age at onset	Treatment	Result
Ellen K.	9 9	Clear	7	33	Good		55543 0–0	4 4	4×4	6	Malaria, As Bi and intracisternal injns.	Alive 1933, aged 33.
Mrs A	897	—	5	06	—		344444443 (Maida Vale Hosp.)	+ + + +	4 4	36	Malaria	Alive and well 193[illegible] aged 54.
2. Jack T	9	Clear	3		Same	+	33344 000 (Westminster Hosp.)	4 4	4 4	$3^{10}/12$	Malaria, As and intracisternal injns.	Alive and well 1938, aged 28
4 Fred T	902	Brother of [illegible] Diagnosed G.P.I. at age 9 at King's College Hospital and died aged) years										Died aged 2.
5 John P	9 9	Clear		0 5	Fair	—	33 0–0	4 4	4 4	$9^{11}/12$	(Malaria did not take.) 4 Sulfoam. T.A.B. acc. Intracisternal injns.	Died aged [illegible] P.M. at National Hospital. ? G.P.I. ? M.V. cerebral syphilis. Mentally like G.P.I.
6 Lilian P	9 5	Clear		5	Good	5	555555443	4 4	4 4	½	Malaria (3 courses). Intracisternal injns. As and Bi.	Died aged 22 7/12. Blood and C.S.F. negative.
7 Gordon R	9	{(a) Clear {(b) Clear	3 3	06	Some Good	—	— 5544 0–0	4 4	4×4 4 4	3^{2} 1 7 2/12	2 years mercury. Then Tryp., N.A.B., Sulfoam, T.A.B. malaria and intracisternal injns.	Blood always 4×4. C.S.F. improved little after intracisternal injns., then relapsed 4×4. Died aged 1/12 septic meningitis after otitis media.
8 Chas R	907	Sl. bld. std.	Slight increase		—		—	4-4	4 4	0	4 Gal)l and mercurialised serum intrathecally	Died G.P.I. aged 14.
Jessie R	905							4	4	9	(Dr Batten notes lost.)	Died G.P.I. aged 12.
9. Robert A.	923	Clear			Good	tr	5555555 00 54322 0–0 in months	4 4	4 4	8½ $8^{3}/12$	Tryp. bismuth, malaria (at Maudsley Hosp.)	Died G.P.I. aged 3 12.

Fred T	9 8	Clear	36	5	Good		5555554?	4-4 4 3-	4×4		Malaria, As, Intracisternal inj.	Spastic diplegia. G P I. Progressing at 13-1 Died when.
2. Ed W	920	Clear	5	5	Sl.		5555443 00	4 4	4 4	8	Malaria, As and Intracisternal injns.	Died aged 8¹¹/₁₂ accidentally Septic meningitis.
Mrs S	90?	Later (942) C S F was typical of G P I at W.E. Hosp at age 28. 4		04			555532 0-0	+30+		8	Malaria (courses) Tryp. (after which she had negative child).	Died aged 34 congenital G.P I
4 M B	9	Done at L C H		07		+	luetic curve	+ +	+ +	3		Died aged 13 early G.P I., septic meningitis.
5 E thn G	92	Clear	34	04	Good		344444 00	4 4	4 4	9½	Tryp., Bi, malaria. Blood and fluid became negative, but died, probably G.P I aged 15½ Fits since 935. (Mother died G.P I)	
6 Geo W	9	Clear	8	05	Same	+	555543 00	4-4-	4 4	2½	(Diagnosed by A. T Pitts from the teeth.) As.	921 symptoms of G P I. Almost certainly dead.
7 Robert B.	9 9	Clear	68	04	Good	17 (N A and Lange never became characteristic)	0-0	4 4	4×4	8½	As and intracisternal injns. Malaria later at Horton. (Mother died G P I aged 43)	Died aged 4½, G P.I The Manor Hospital, Epsom.
8 Geo L	9	Clear		06	Good	3	5555543?	4×4	4 4	8⁷/₁₂	As, T.A.B. (8,775 mils)	Luton Infirmary Died (almost certainly G.P I) aged 9¹/₁₂.
9 Mary W	9 3	Clear	35	08	Good	3	55555432	4 4	4×4	8²/₁₂	Tryp Bi and As at R.N H. Epidemic fits. (Mother died G P I.)	G.P.I almost certainly and dead by now.
10. Irene W	920	Clear	8	06	Good		555555544 (becoming almost negative in 6 months)	4 4 to neg. in 10 years	4×4 to neg. in 5-6 years	0¹¹/₁₂	Spastic legs. Mother died. Dr Schlesinger diagnosed syphilitic pachymeningitis and myelitis. Mercury 2 years. Tryp., Bi, malaria, N.A.B. Mynah serum, Ovarian	Emotional, fat; at 21 looks aged 16 (942) (see p. 309). Could not trace in 95

Note With the exception of case 8, who was treated with intraspinal injections of mercurialised serum, all who were given intracisternal injections received salvarsanised serum (see p. 3 5)

some months later and shortly after that a second course of intracisternal injections. A few weeks later the child had improved so much that she had become clean in her habits, took her food well and was able to play in the garden with other children. She even remembered things that she had done at home, remembered going to school and things the teacher had taught her.

To conclude the history of the case, we may say briefly that the C.S.F. became quite negative, as also did the blood, at the age of 10 years (1929) and they have remained negative ever since. *In spite of all efforts it has been found* impossible to educate her and at present she is in an institution whose medical superintendent recently wrote me: "The patient is alive and well. She is 30 years old with a mental age of 4 and is an efficient folder in the institution's laundry." *At 33 years of age (1953) she was in the same condition.* As a result of one's experience in this case one is inclined to the opinion that in so young a child it does not appear to be worth while to treat the condition, certainly not by the methods which were at our disposal at that time. Even should one *succeed in staying the activity of the treponema, the damage to the parenchyma* of the brain appears to be irreparable. It might, however, be worth while trying the effects of malaria together with artificial heat therapy and penicillin in a similar case.

Mrs. A., a congenital G.P.I. who started at the age of 35–36 years, exhibited the following features on investigation: "Her memory was faulty, there were severe headaches accompanied by vomiting and often with a dead feeling in the *left arm and side of the mouth, she was euphoric, lacked insight, her attention* was poor and speech was slow and dysarthric. The pupils were normal. The C.S.F. contained 52 cells per c.mm., protein 0·06%, Lange 3444444321, W.R. strongly positive." She was treated with malaria. Three years later her doc*tor reported that she appeared to have recovered, had no further signs of G.P.I.* and the W.R. was said to be negative.

The family history was interesting. The patient's parents had 12 or 13 children of whom only 4 survived. Her father died of G.P.I. after an illness lasting 3 years. *Two older brothers of the patient had mild I.K., one of them* starting at the age of 36, which curiously enough was the age at which Mrs. A. started her G.P.I. Of her own 2 children, the first is said to have been a very small baby weighing only 4 lb. (1·8 kg.) at birth. He had a double hernia and was under the doctor *for the first 6 to 9 months. His blood may have been* positive in infancy but it was not examined. When he had his blood tested at 11 years it was negative. His brother born 6 years later was a healthy baby but had a largish square head which may have been due to a mild hydrocephalus or it may have been *a family trait, because his mother had a head almost exactly* similar (Fig. 88). This boy had haemoglobinuria at the age of 3 and his W.R. *was strongly positive at 5 years of age* and on several subsequent occasions during treatment. He later returned to his own doctor for treatment, who informed me that the W.R. *had become negative at the age of 10 years.*

Our third surviving case of G.P.I. occurred in a boy who was born in June 1910. He had infantile symptoms of congenital syphilis with epiphysitis in the arms and legs and was given the *usual mercury treatment which* consisted of inunctions for 7 years. At the end of that time his blood W.R. was still strongly positive and injections were started at the age of 8 years, but unfortunately the treatment was very intermittent and irregular. At 11 years of age his right pupil was much bigger than *the left; at 12 he developed polyuria, and at 13* the pupils were noted to be equal in size. At 14 years of age they had again become un-

equal and it was then that the C.S.F was examined. Cells were 30 per c.mm. protein 0·1% N.A. positive Lange 2334410000. As the boy was too old to be admitted to our ward he was taken into the Westminster Hospital under the care of the late Sir James Purves-Stewart, who kindly undertook the further treatment. The lad was given two courses of intracisternal injections of salvarsanised serum as well as a course of malaria. The symptoms about this time were deficient concentration and he was euphoric and loquacious at the age of 16½ years. The pupils remained unequal in size and at the age of 20 were found to be inactive to light. At the age of 23 he was apparently very well and his blood and C.S F were both normal. At the age of 24 he was passed into the Army although the pupils were still slightly unequal and the right failed to react to light. He was last seen in 1938 when he was 28 years old he was then quite



(a)



(b)

FIG 88

A congenitally-syphilitic mother and child both showing frontal bossing The mother had G.P I., the child haemoglobinuria

well except for recurrent boils which he had contracted in Palestine. It is of interest to add that his brother developed G.P I at 19 years and died at the age of 22.

Several of our cases are of the text book type, others show interesting divergences from it.

One patient (L.P) was brought up to the Outpatients Clinic, a short and stocky girl, rather fat and with spade like hands. She was suffering from fits at the age of 11½ and her pupils were unequal. She was diagnosed by the physician in charge as being possibly a case of hypopituitarism. She was given a course of malaria and intracisternal injections, after which the blood and spinal fluid became quite negative at the age of 16. At 20 she went to a nerve hospital, where her condition was diagnosed as epilepsy and amentia," and she died eventually at the age of 22½ the death certificate certifying chronic epilepsy syncope and bronchopneumonia as the causes of death with no mention of

congenital syphilis, though this information and the treatment the patient had received from us had been given to the hospital authorities. (Table 19, case 6.)

Another patient (E.G.) whom we first saw at the age of 9 years was sent up by her family doctor because she had always been backward and she found it "difficult to walk or to stand still." On admission she was fairly well-developed, had typical Hutchinsonian teeth, which had apparently escaped the doctor's recognition, was emotional and very apastic in her movements, so that she could hardly walk. Her hands and tongue were tremulous and the eyes showed marked choroido-retinitis with macular pigmentation. Knee jerks were doubtfully increased. She was given a considerable amount of treatment with tryparsamide and bismuth, malaria and neo-arsphenamine. The pupils became more sluggish in their reaction to light. Later on, the patient seemed to have benefited by the treatment; in fact an aunt who brought her to the clinic on one occasion said that "she was becoming quite witty." The improvement was only temporary, for at the age of 14 she started having fits and by 19 as she fell about very easily she had to be placed in an institution, in which she remained until her death at the age of 25½. The death certification was "general debility, wasting, congenital idiocy," again without any reference to the prime cause of death, namely congenital syphilis. In the absence of a post mortem it is difficult to say whether there were anatomical lesions of congenital G.P.I. present, but during life the condition was regarded as such. It is of interest to note that the patient's mother had died of G.P.I. at the age of 38. (Table 19, case 15.)

Robert B., born 1919, early history was indefinite. He started having fits at the age of 8 years; at 9 years he suffered from fits of temper, frontal and later occipital headaches and developed a marked squint. He was found to have a positive blood and C.S.F. and was given a course of intracisternal injections, after which the C.S.F. improved, as did also his general condition, and he was able to attend school again, which he did regularly without any complaints as to his conduct. A year later he was again brought up to Great Ormond Street in a fit and some months afterwards he became troublesome and had to be sent into an institution. There he had violent outbursts and became dirty in his habits. He deteriorated very rapidly and was sent to an institution for mentally-defective children, where he was diagnosed as a typical congenital general paralytic. On admission he was "confused and rambling in his speech, restless and dazed, could not converse rationally, had outbursts of temper, used obscene language, was dirty in his habits and could not wash or dress himself." He was given malaria, but his condition went from bad to worse. He died, after various convulsive seizures, at the age of 14½. (Table 19, case 17.)

Mary W., who is said to have had no infantile symptoms and later fell about a good deal, having, as her mother said, "a bad balance," appeared to be otherwise well until the age of 6½ when she developed epileptiform seizures. These she had on and off until she was last seen at the age of 17. She started menstruating at 9 years of age. She showed marked syphilitic eye changes and before she was 10 she developed a status epilepticus, becoming much more mental. She became very fat, with marked mammary development, and at the age of 11 years she weighed 10 st. 7 lb. (66·6 kg.) and at 13½ years, 13 st. (82·4 kg.) (see Fig. 91). She was regarded as a case of hypopituitarism. It is of interest to record that this patient's *mother also died of G.P.I.* (Table 19, case 19.)

One other patient in this category (I. W.) who had a typically paretic

C.S F may possibly have been a congenital G.P I She was last seen at 21 years of age when her physical condition was fair but she was mentally weak

I.W was born in Nov 1920. She was brought to Great Ormond Street and came under the care of Dr Schlesinger at the age of nearly 11 years. She then complained of losing the use of her legs and walking stiffly There was no history of syphilis in either parent and the child was the outcome of the first pregnancy Rash and snuffles were present from two months of age. There was no epiphysitis or marasmus. On the birth of a brother 7 years later syphilis was diagnosed in him, and Irene was then examined and found to be positive and given two years treatment with mercury She had always been rather mentally deficient, and at about 9 years of age she began to walk stiffly and to lose the use of her legs. On examination the gait was found to be spastic there was a tendency to kyphosis and forward drooping of the head. The lower limbs were spastic, with increased knee and ankle jerks. There was a double extensor response and no Romberg's sign. The upper limbs showed some spasticity of the right arm jerks were normal. There was no nystagmus, the pupils were unequal and the fundi normal No intention tremor was present. There was thought to be some impaired sensation to pin-prick in the legs and the suggested diagnosis was syphilitic myelitis and pachymeningitis. The teeth showed only slight Hutchinsonian and Moon characteristics. The S.W.R. was strongly positive and the C.S.F was also strongly positive with protein 0·06% cells 8 per c.mm., N.A. 2 and the Lange curve typically paretic. After a year's treatment with tryparsamide and bisoxyl and walking exercises she showed some improvement in her blood and C.S.F but her physical and mental condition were not improving She was then given malaria. After much treatment with tryparsamide, trivalent arsenicals and orarsan the blood and fluid became negative, and the blood was still negative at the age of 21 years. She was then able to walk fairly well, but was unable to concentrate, was undersized and looked about 16. She had menstruated regularly since the age of 13. (Table 19, case 20.)

It is interesting to note that although the case was one affecting mainly the spinal cord, there was in addition evidence of cerebral damage in the mental retardation and the inequality of the pupils.

Symptomatology of congenital G.P.I Apart from the infantile and early type of case, which can only doubtfully be regarded as true G.P I there are the two groups, as previously mentioned which may start abruptly but more often do so insidiously Even when the patient's friends give a history of sudden onset this may be incorrect, as in the case of Ellen K subsequent inquiry of her schoolmistress eliciting the fact that already during the previous 5 months the child had begun to show signs of abnormal mentality She was restless and apathetic, inconsequent in her behaviour and on one occasion she had a very unusual screaming fit when brought into school and later took to slapping the other children She was inattentive and unable to concentrate sometimes when asked a question she did not give the reply but just repeated the question itself In spite of this the history given by the parents was that having been apparently well she was late in coming home from school one afternoon,

congenital syphilis, though this information and the treatment the patient had received from us had been given to the hospital authorities. (Table 19, case 6.)

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Ataxy which may manifest itself by an awkward gait and inco-ordination of the upper limbs, may also occur we noted this symptom in 3 of our patients. Stewart has drawn particular attention to this symptom, which he regards as one of the earliest motor signs, and he believes it to be more often an indication of cerebellar degeneration than of involvement of the posterior columns of the cord. In congenital G.P I the tendon jerks are usually exaggerated, with extensor plantar responses in some cases. With the advent of taboparesis the knee jerks disappear and incontinence of urine may occur though Ferguson and Critchley noted early sphincter disturbances, including retention, incontinence and precipitancy of mic turition, in more than half their cases of congenital G.P I uncomplicated by tabes. Epileptiform seizures are frequent during the course of con genital G P I, or as we have previously observed, they may occur at an early stage of the disease and antedate the later manifestations by months or even years. As the disease progresses gross choreiform movements may be noted the patient becomes bedridden, contractures develop and emaciation occurs. He lies huddled up bones almost protruding through the skin, so that it is impossible to prevent bedsores, and the patient ultimately succumbs to hypostatic pneumonia or general septic infection.

The author saw some examples of this type of congenital G.P I at the Wakefield Asylum in 1911 and 1912, and the picture presented by these unfortunate patients was almost identical with that seen in patients in the last stages of sleeping sickness in Uganda. The pathological anatomy of the two diseases is very similar a wasting of the grey matter of the frontal and central lobes of the cerebrum associated with degeneration of the pyramidal cells, perivascular round-celled infiltration and marked increase of glial tissue, due in the one case to the *Treponema pallidum* and in the other to the *Trypanosoma gambiense*

Pathology of congenital G.P.I The pathology of the condition is in the main very like that of the adult form of the disease, namely atrophy of the brain with dilatation of the ventricles and granulation of the ependyma. Microscopically there are characteristic inflammatory and degenerative changes in varying degrees. The reduction in size of the cerebral hemi spheres may be due in part to the chronic wasting of the cortex of the brain and, possibly in greater measure, to an actual developmental arrest of growth. Changes similar to those seen in the cerebral cortex may be found in the cerebellar cortex, to which Sträussler was the first to draw attention, and he likewise noted the frequency with which the cells of Purkinje displayed two nuclei. There is very marked increase of neuroglia and microglia, and the treponema may be demonstrable by Jahnel s stain, sometimes in large numbers. In many cases syphilitic lesions, particu larly in the form of increased fibrosis, may be found in the internal organs, and in a considerable number of cases atheromatous lesions, or patches of fatty material resembling atheroma, may be found in the larger blood

vessels aorta, carotid, etc. Hypoplasia of the sex organs and of other endocrine glands may occur and juvenile paretics frequently exhibit a hypoplastic constitution and, in consequence, varying degrees of infantilism (Mott Nicol, Haas and others).

Diagnosis This depends on the four usual factors—history mental picture, the neurological signs and the blood and C.S.F investigations. The early and mentally-defective group of cases may be difficult to diagnose with certainty even at autopsy and it is probable that most of them are cases of meningovascular syphilis with secondary cerebral degeneration. The mental symptoms in the older congenital paretics are more indefinite than in the adult type of case, so that the congenitals cannot be divided into clinical types Added to this the many and varied neurological manifestations, as recorded in our 20 cases, make the diagnosis more difficult. We were unable to follow our cases through to the end and several of them died in institutions where post-mortem examinations were not performed and the causes of death were, to say the least, rather questionable. Even an autopsy would not always provide a certain diagnosis, for Nicol and Hutton record that of 7 post mortems they carried out, only 4 gave undoubted evidence of G.P I two had meningovascular syphilis and the seventh case was ? epileptic, ? congenital G P I The blood and C S F would always give a positive W R. the C.S F would also show the cardinal changes of a paretic fluid with however fewer cells per c.mm. than in the adult type.

The diagnosis in the very early cases may have to be made from idiocy epilepsy meningovascular or cerebral syphilis and cerebral tumour and in the later cases from encephalitis lethargica, disseminated sclerosis and various psychoses.

Prognosis It is hopeless in the infantile type of case to expect a cure Two of our cases survived for 17 and 20 years, spent in institutions. In the type of case which supervenes upon some years of normal mental development, the older the patient is when the symptoms manifest themselves the better is the outlook, provided the condition is recognized early and is efficiently treated Patients who become affected early in childhood as did our patient E.K at 6 years of age, and who was given intensive treatment with malaria, arsenic, bismuth and intracisternal injections which as above recorded cured her syphilis and arrested the cerebral degeneration, practically always show retardation or arrest of mental development though their physical condition may be commensurate with their age E.K. at the age of 30 looked her age mentally she was estimated at 4 years Some of the older treated patients may improve to a varying extent so that they are able to carry on even intellectual pursuits though showing a little evidence of some psychic disorder[1] in others the condition may

[1] Dr Nicol formerly Director of the Mott Clinic at Horton Surrey has informed me of an interesting family he once had under his care in which both

be arrested with the patient's mentality permanently impaired while some deteriorate despite all that is done for them.

Treatment Doubtless penicillin should be given as soon as the condition is diagnosed but I know of no reports as to the results of its use in congenital G P I It should be used in conjunction with malaria and other forms of treatment mentioned above, and in my view treatment should not be relaxed until blood and C.S F are both W R. negative and the fluid is normal in all other respects.

Congenital tabes

This is distinctly rarer than congenital G.P I at the most we have encountered but 7 cases in our series and in one of these the diagnosis was not absolutely certain Ferguson and Critchley report 8 cases of tabes in the 50 cases of congenital neurosyphilis included in their paper Its incidence between the sexes was equal, which they say is the usual experience. The average age of onset was 17 years, the extremes being 10 and 24 years They gave as the chief points of importance in congenital tabes the age of onset, which is about puberty with failing vision and paraesthesiae as the first symptoms ataxia and lightning pains are rarely complained of but headaches, photophobia and diplopia are common later symptoms. Sphincter troubles were uncommon in their patients, and apart from slight mental dulling no psychological changes were noted Ataxia and loss of sensation are slight compared with the findings in adults. Nystagmus was present in 3 cases, strabismus in 4, pupil anomalies in all 8 cases, with dilatation in 4. Optic atrophy was also common, so also was absence or diminution of the tendon jerks Trophic disturbances were rare and the authors reported no gastric crises, although from the literature these are regarded as fairly common. Serologically the blood W R. was positive in all their cases The C S F gave a positive W R. in all cases but one which was normal in all respects.

Worster Drought (1924) showed a case of juvenile tabes dorsalis in a girl of 10 at a meeting of the Royal Society of Medicine and at the same time a case of early Friedreich's ataxia for comparison. He pointed out that the similarity between the two diseases is the loss of knee and ankle jerks, and while a juvenile tabetic has Argyll-Robertson pupils but no ataxy the patient with Friedreich's disease shows general muscular incoordination with an ataxic gait and normal pupillary reactions.

In our own series of 7 cases the age of onset was between 8 and 10 years in 5 cases, at 19 and 35 years in the 2 adult cases In two of them, one a girl who started at 8 and the other a man who started at 35 the initial symptoms were primary optic atrophy with sensory disturbances, but

father and son suffered from G P.I the latter of the congenital variety He did well on the usual modern treatment of G.P I and was able to carry on a useful occupation, though at times he showed signs of some psychic disorder

later both patients developed mental symptoms, so that the cases had to be classified as taboparesis As with G P I it must be borne in mind that congenital tabes may start in adult life, even as late as the third and possibly the fourth decade. The first complaint of the patient is, as a rule, in connection with vision, and on ophthalmoscopic examination this is found to be due to optic atrophy Other signs are inequality of the pupils and their failure to react to light. Sphincter troubles were not observed in any of our cases, but enuresis has been described by several observers as being an initial symptom of congenital tabes dorsalis as, however enuresis may be due to commoner causes than tabes, it is very likely to be overlooked as a symptom of this syndrome in young patients Gastric crises and girdle pains are definitely rarer than in the adult type of the disease. Lightning pains may occur in a small proportion of the cases, while trophic disturbances such as Charcot's joints are very rare. As already mentioned, two of our patients subsequently developed psychical changes, so that they had to be regarded as taboparetics and owing to the fact that the war prevented our following up the other cases, it is impossible to say how many of the others, if any subsequently showed signs of paresis. Congenital tabetics may show remissions often of some years duration accompanied by return of the blood and C S F to normal The impairment of vision though it may participate in the remission, rarely if ever shows any permanent improvement.

The following points of interest emerge from the histories of our 6 (? 7) cases of tabes dorsalis. The 6 undoubted cases gave positive blood reactions (W R.) and 5 of those whose C S F was tested gave positive results with the fluid. Three of the 6 juvenile tabetic patients had chorioido-retinitis and in two of these the original diagnosis was primary optic atrophy while the third patient is stated to have had chorioido-retinitis from early life until the age of 21 years, when he became quite blind He was a congenitally-syphilitic father in whom the clinical diagnosis of congenital tabes was made by Dr (now Sir Francis) Walshe at University College Hospital where the patient was examined He had dilated fixed pupils the knee and ankle jerks were absent. His S W R was positive the C S F was not investigated.

One of our patients in whom the original diagnosis of primary optic atrophy was made was very interesting

He was the second of 5 children in the family and the only one with a positive W R. when the children were tested at 11 9 7 5 and 3 years of age respectively Both parents were at this time in a mental hospital suffering from general paralysis so that early histories of the children were not obtainable The boy (D H) attended an eye hospital on account of defective vision at the age of 7½ years. His S W R was positive and the diagnosis of his condition was bilateral optic atrophy He was not treated but referred to a special hospital for nervous diseases which he attended at the age of 8 years. The notes at this hospital gave his complaint as "weak sight and falling forwards in the dark." On

examination there were noted frontal bossing doubtful Hutchinsonian teeth, irregular pupils and primary optic atrophy." The diagnosis was congenital tabes dorsalis. He improved considerably with treatment, bismostab, potassium iodide, stovarsol and mercury rubbings. As the parents had by this time developed general paralysis, for which they were hospitalized, and the children were consequently dispersed, the patient was admitted under my care at the London County Council Congenital Syphilis Unit at St. John's Hospital at the age of 9⁴/12 years. On admission the left pupil was much bigger than the right and was fixed. Vision with the R.E. was very poor <6 60 and not too good with the L.E., 6/60. The eye specialist at this hospital thought the discs showed secondary optic atrophy It would appear, therefore, that in some cases the experts may differ as to whether an optic atrophy is primary or secondary [1] His S.W R. and Kahn were strongly positive. The C.S.F was clear cells 18 (16 mono., 2 polys.) per c.mm., protein 0·04% N.A. 1 W.R. 4·4·4·0., Lange 01110–0. After treatment with sulphostab tryparsamide and bismoxyl the blood and C.S.F became normal well within a year and remained negative, and there was no progression of his tabes at the age of 11½ years at the outbreak of the second world war After the war he was discovered at the Royal Blind School at Leatherhead, where he had become an inmate in 1944, was taught brush making and later became a journeyman in the employ of the School (1951).

Our one doubtful case of tabes dorsalis occurred in a girl of 10⁸/12 years.

She had incontinence of urine and faeces, and attacks of vomiting which it was considered might be due to gastric crises. On examination her knee jerks were absent, the blood and C.S F normal. The fundi were normal, but our ophthalmologist Mr Doyne detected old corneal scarring of the right eye, not typical of interstitial keratitis. There was no optic atrophy but from the symptoms related above Dr W G Wyllie, our neurologist, came to the conclusion that a probable diagnosis was tabes dorsalis. The girl s mother was syphilitic.

Congenital Taboparesis

Although neurologists have for many years recognized the occurrence of taboparesis as a sequel to acquired syphilis, the published records prior to the year 1929 of congenital G P I and tabes do not differentiate congenital taboparesis. Ferguson and Critchley (1929 and 1930) were apparently the first to refer to this condition which they diagnosed in no fewer than 12 of their series of 50 cases of congenital neurosyphilis. Of the 12, 7 the authors say would have been regarded as G P I but for the absence of the tendon jerks, and in 4 of these the C S F showed a typically luetic Lange curve On the other hand, 3 of the cases would have been regarded as tabes dorsalis but for the presence of fits, tremors speech disturbances and mental changes in varying combinations in the 3 patients. Of the other 2 cases in this category one was regarded as typical tabes dorsalis when first under observation, but shortly after discharge from hospital

[1] In this connection the monograph by Prof Bruetsch is of interest. H maintains that "primary" optic atrophy is misnomer since degeneration of the optic nerve fibres is the result of syphilitic inflammation and therefore always secondary "

she began to show marked psychological changes and mentally she became a typical general paralytic. It is of interest to note that this particular patient had Charcot joint changes in her spine. The twelfth patient in this series was mentally normal, but had tremor of the face tongue and hands, speech defects and absent knee jerks. The C.S.F contained 27 cells a positive globulin reaction and a mild Lange curve (0012331000)

The adult taboparetic in our series was a man who presented as a case of tabes, a brief account of which is as follows

R.W., born 1903 was first seen at the age of 35 by Dr J C. Hawksley and diagnosed by him as being a congenital tabetic with shooting pains in the legs. Right eye pupil small and fixed. Left eye had been removed in childhood for an injury Knee jerks were absent and Romberg's sign positive. The blood and C.S.F were both positive when he was first seen at the Connaught Hospital. For a time he improved under treatment, but some years later his condition deteriorated and he was removed to a mental home Here his blood and fluid were again examined. The W R. was strongly positive in both and the C.S F showed cells 134, globulin increased, Lange 4444321000 (1943). After malarial treatment he is said to have made an excellent recovery and returned to his work, which he was able to carry on satisfactorily for a year He then became thin developed slight defect of speech slight tremor of the lips and tongue all tendon jerks were absent and he had analgesia of the lower limbs. The W R. was less strongly positive in the blood and fluid, and in the latter the cells were now only 7 and the Lange 5554433200. His condition had changed to taboparesis. The patient did not wish any further treatment at the time, as he was actively carrying on his business. Subsequently however he was given a course of penicillin injections to which he responded satisfactorily so that he was still able to work albeit at a reduced tempo 13 years after the onset of his illness. It is of interest to record that his father died of taboparesis with ulceration of the right big toe R.W's child, born 1931 had no infantile or later symptoms. Teeth and eyes were good. W R. was negative, as was also her mother's.

It would appear from the literature that taboparesis is more likely to supervene in congenital tabetics of early adult age as was the patient R.W than in juvenile congenital tabetics

Neurotropism *v* familial vulnerability of the central nervous system

It has long been the opinion of some syphilologists that there are two strains of the treponema—a dermotropic and a neurotropic. The position was fairly stated by Harrison (1931) when he came to the conclusion that in all probability familial predisposition was a more important factor in the development of neurosyphilis than was the presumed existence of two types of treponema. Many authorities share Harrison's view and my own observations would appear to support it In several of our families there has been neurosyphilis in 3 generations in other families 2 or 3 of the children have suffered from neurosyphilis in many cases one or other parent having been similarly affected These observations by themselves

might support either assumption, but conjugal neurosyphilis would favour the assumption of the existence of a neurotropic strain of treponema, as Levaditi and Marie had suggested in 1919 after their investigations on general paralysis. Jeans and Cooke (*op cit.*, p 185) came to the conclusion that the tendency for the treponema to localize in the nervous system was probably not dependent upon any selective affinity of the treponema for the nervous system, but on certain unknown racial familial or individual properties.

Conjugal syphilis

Hutton (1941) found the incidence of familial neurosyphilis sufficiently high to justify the investigation of all marital partners This aspect of neurosyphilis (conjugal neurosyphilis) was studied by Kemp and Poole (1925) and by Nicol and Hutton (1936 to 1944) when they found that the incidence of presumably conjugal G.P I tabes and taboparesis was particularly high.

That the white race is more predisposed to neurosyphilis than the non-white is well known and the fact that certain members of a family are picked out by neurosyphilis seems to suggest that there are individual variations in resistance to the invasion by the treponema. As tentative suggestions to explain this variation in individual resistance one might mention the opinion which has long been held that insufficient early treatment, particularly arsenical, may be a cause of the invasion of the C.N S and certainly in many of my cases the children had undergone mercurial treatment, which was usually of a very perfunctory nature, especially in the case of hospital outpatients. Another possible explanation may be variations in the structure of the patient s proteins (Dodds 1950)

The nervous child

Certain French writers and the Colombian writer Torres-Umaña (1935) have stated that the children of syphilitic parents may possess an unstable nervous system, which is manifested in various ways, as by headaches insomnia, excitability of temper untrustworthiness, fidgetiness, enuresis, hysteria and mild choreiform movements. We have had instances of this kind amongst the children of syphilitic parents and even if the child should have had a positive W R. it was difficult to decide whether the symptoms noted were really attributable to the syphilitic infection. Should the child improve on antisyphilitic treatment it might be justifiable to conclude that the symptoms were due to the syphilis but personally one would be more inclined to think syphilis was the cause if the child s spinal fluid were abnormal. The problem is practically insoluble and it would depend upon the predilection of the particular observer whether the symptoms were regarded as syphilitic in origin or otherwise.

Behaviour problems and psychiatric manifestations

We have had several children in whom psychical manifestations were the only sign or symptom of an otherwise latent neurosyphilis. For example, one child appeared somewhat precocious and used to swear like a trooper She also made a tremendous fuss and screamed before each injection, and was very naughty in the ward because she used to steal the other children s toys and put the blame on someone else. She was neurosyphilitic and under treatment her behaviour improved remarkably Another neurosyphilitic patient used to steal money from his mother s purse at the age of 9 but non-syphilitic children have been known to do the same.

The possible relation between parental syphilis and character defects, behaviour problems and psychopathic tendencies in the offspring has been debated by authorities for many years. Fournier Hochsinger Hutinel Nonne and others have all referred to the effects of syphilis upon the descendants, but they gave no statistics in support of their views. Haines (1916) found that nearly 21 per cent of 365 delinquent children had a positive W R Bazeley and Anderson in Boston (1915) studied the subject from rather a different angle by analysing two groups of 60 delinquents, one group syphilitic and the other non-syphilitic, with the result that they found no very striking difference between the various misdeeds of the two groups The Solomons, who quote these studies, think, however there is an indication that it is worth while considering the possibility of congenital syphilis in the case of all juvenile delinquents. I have long held this view and in the 1920 s advocated to the authorities that before young offenders were punished or sent to an institution, they should be tested for the presence of congenital neurosyphilis but the suggestion was not very sympathetically received and I do not think it was acted upon. I ventured to suggest that if the C S F were found positive they should be appropriately treated for their neurosyphilis, together with the social measures for dealing with delinquency In view of further experience I would recommend that the parents and other members of the family should also be investigated as the delinquent himself might conceivably not have a positive W R. or any stigmata of the congenital disease and nevertheless come from a syphilitic stock. Such investigations, which should not be impracticable, would also help to reduce the incidence of congenital syphilis and of many cases of mental deficiency and psychosis themselves the result of the acquired disease.

Mental deficiency

When we come to the relation between congenital syphilis and mental deficiency we are on more secure ground Most authorities now agree that syphilis is a cause of mental deficiency the main disagreement being

as to the actual percentage of cases in which syphilis may be the causal agent. As was pointed out by H R. Dean many years ago, the percentage would be influenced by the age at which the child's blood was examined The younger the child the more likely would the serum reactions be found positive, and Dean observed that at about the age of 16 a very marked reduction in the percentage of positive blood reactions of mentally-defective children took place. Another point to be remembered in this connection is that the parents and sibs of a mentally-defective patient should all be examined from the point of view of syphilis, because they might show evidence of the infection either in the blood or in the form of stigmata, whereas the patient himself might have a negative W.R. and no stigmata of the disease. We must also bear in mind the fact that it is not essential for the treponema to be transferred to the patient because parental syphilis may undoubtedly give rise to retarded cerebral and mental development. In addition the mental deficiency might result from lesions definitely inflammatory (meningitis, hydrocephalus, encephalitis, neuritis), as well as from meningovascular lesions. Mutism and deaf mutism could be produced in this way and I have on two occasions seen deaf mutism in the negative child of a syphilitic mother Here, again, it was impossible to be dogmatic about the causation of the condition it may have been a coincidence.

Stewart (1925) investigated 800 patients in the Leavesden Mental Hospital, the inmates of which were low-grade mental defectives with physical infirmity including paralysis of all types, blindness and deaf mutism. Of the 800 patients examined, varying from 6 to over 40 years of age 642 gave negative Wassermann reactions, of which 42 showed unequivocal signs of congenital syphilis, so that of the 800 examined exactly 600 or 75 per cent were non-syphilitic and 200 or 25 per cent syphilitic. It is significant that 42 of the cases gave negative blood tests, yet many of these had been positive in childhood according to the case reports, thus confirming Dean's early observations. Stewart found that the stigmata of congenital syphilis, in those patients whose Wassermann reactions were negative, were in many instances remarkably pronounced, from which he was inclined to speculate that the more severely the body is damaged by syphilis in infancy the more likelihood is there of the infection dying out in later years.

Precocity

One of my early cases (1919) showed marked precocity which focused my attention upon this feature as a possible sign of congenital syphilis and induced me to look out for similar cases in the future. I have notes of 10 cases of precocity in congenitally-syphilitic children, 2 of them being sisters.

On going into the literature, I found that Jonathan Hutchinson in 1863 had remarked that one of his cases was precociously intelligent Hughlings Jackson (1875), in the case of juvenile G.P I above referred to remarked that as a child the patient was rather precocious, talked early learned to read and write early was fond of reading music and was very *religious*. Jackson considered these achievements as evidence of a precocious cleverness rather than of intelligence, a style of ability quite consistent with a want of a high and robust intellect. Mere cleverness is no good sign of mental superiority on the contrary precocious cleverness in children is an evil sign Judson Bury (1884) recites the two foregoing cases and adds one of his own in a female aged 11½ who died with typical signs and symptoms of congenital G P I The Solomons (1922) remarked Some congenital syphilitics are unusually precocious and have a high mental rating In their view this does not indicate that the syphilitic heredity is an asset or that it is the cause of precocity but merely that the syphilis had no deleterious effect upon the particular child s mentality

In this connection it should *perhaps* be mentioned that *precocity* may take one of two forms the more common being a mental or psychical precocity and the less common a physical or sexual precocity Of the 10 cases which came under my own observation 8 were instances of mental and 2 only of sexual precocity Of the 8 3 were cases of neurosyphilis and a fourth, whose fluid was negative at the age of 3 subsequently (at the age of 20) became mentally peculiar Amongst the 8 was a girl N O who is more fully referred to in the section on the Endocrine Glands as a patient with physical infantilism who from an early age was able to act in pantomime.

The cases of sexual precocity were two girls with neurosyphilis who menstruated at the age *of* 9 and did so *regularly* thereafter One had congenital tabes and maintained a strongly positive blood and spinal fluid until the age of 13 The other (M W) is referred to on p 377 as a case of ? hypopituitarism and fits, and occurs also in the account of congenital G P I

Chorea

Jonathan Hutchinson in his monograph (1863) refers to a patient with congenital syphilis (case 6 p 170) who had interstitial keratitis at 6 years St. Vitus s dance at 14 a syphilitic tongue and other manifestations."

Many authorities, particularly French and Italian, have regarded syphilis *as a possible cause of chorea*, and both Mott and Nonne held the view that choreiform movements and true chorea might occur in children whose parents were syphilitic Mettler (1903) discussed syphilis as a cause of chorea and concluded that in rare instances syphilis might be a cause In 1945 Weckhardt, writing on *Chorea syphilitica* indicated that the cases reported in the literature seemed to fall roughly into three groups

(1) Acute dyskinetic episodes resembling Sydenham's chorea in congenitally-syphilitic children
(2) Hemichorea associated with either congenital or acquired syphilis and
(3) Chronic progressive chorea resembling the hereditary type of Huntingdon associated with acquired syphilis.

The cases in Group (1) were all congenitally-syphilitic patients between 7 and 16 years of age. In each recorded case the disturbance ran its course in a few weeks. Improvement or cure after antisyphilitic treatment is mentioned by all the authors he referred to but this must not be regarded as conclusive evidence of a syphilitic causation

In my own records there are 11 cases in which the patients are said to have had chorea or to have twitched, grimaced or been fidgety These cases fall into two groups, A and B Group A, the larger group in our experience, is that in which the chorea-centre in the brain is affected by syphilitic vascular disease or by a presumed syphilitic toxin, and which presumably may be amenable to antisyphilitic treatment. Group B would include cases of typical chorea occurring in a congenitally-syphilitic child. We have not had many such cases under our observation, but an interesting one (I.S.) is recorded on p 127

The other case of interest, which was probably in Group A, concerned a boy who was born in 1908

He was an inpatient under the care of Dr Voelcker complaining of "twitching, ? chorea." He improved very rapidly under injections of N.A.B and his blood quickly became negative. His case is rather of interest because his mother married 2 syphilitic husbands by the first she had 2 stillbirths and a miscarriage and he then died of G P I By the second she had the patient and this husband had been an old soldier in India and his W R. when examined at that time was strongly positive. The mother's blood was not very strongly positive and it is a moot point as to which treponema infected the boy I think it was probably the first husband's disease which the wife had contracted, and that the second husband's infection was such an old one that probably it was no longer infective to the wife or the boy

Arsenic has been used in the treatment of chorea for a very long time and the fact that injections of arsphenamines benefit a patient would be no proof that the chorea was of a syphilitic nature. Certainly the case of I.S suggests that in the event of a patient not responding well to the ordinary treatment for chorea and rheumatic heart, the S W R. should be tested.

Mongolism

Mongolism has long been the subject of speculation and research and in addition to its purely medical interest from the point of view of its

On going into the literature, I found that Jonathan Hutchinson in 1863 had remarked that one of his cases was precociously intelligent Hughlings Jackson (1875) in the case of juvenile G P I above referred to, remarked that as a child the patient was rather precocious, talked early learned to read and write early was fond of reading music and was very religious. Jackson considered these achievements as evidence of a precocious cleverness rather than of intelligence, a style of ability quite consistent with a want of a high and robust intellect. Mere cleverness is no good sign of mental superiority on the contrary precocious cleverness in children is an evil sign. Judson Bury (1884) recites the two foregoing cases and adds one of his own in a female aged 11½ who died with typical signs and symptoms of congenital G P I The Solomons (1922) remarked Some congenital syphilitics are unusually precocious and have a high mental rating In their view this does not indicate that the syphilitic heredity is an asset or that it is the cause of precocity but merely that the syphilis had no deleterious effect upon the particular child s mentality

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Ferguson and Critchley discussed the subject of congenital syphilis and mongolism, although they themselves found no mongols in their series They also referred to an observation of Van der Scheer that the not infrequent mongoloid appearance of some congenitally-syphilitic patients might lead to making an erroneous diagnosis

My own series of congenitally syphilitic patients furnished 4 mongol and mongoloid types of case. Two of them both boys, were typical mongols. One had a fissured tongue, high arch to his palate and long upper incisor teeth. His blood and C.S F were both strongly positive, and remained so in spite of fairly intensive treatment with neo-silver salvarsan and mercury iodide over a period of 3 years. He was then given malaria treatment and tryparsamide, so that at the age of 15 his blood and fluid were normal. He was somewhat mentally defective and also hard of hearing which the aurist reported to be due partly to middle-ear and partly to internal ear causes. The mother had Argyll Robertson pupils and died 5 years later but the cause of death is not recorded. The other patient, Tommy S is referred to on p 376 He had big hands and suffered from polyuria, which suggested a possible pituitary lesion. His face was mongoloid and the little finger curved in the characteristic manner with mongols. His C.S F was negative. The other two cases of the mongoloid type were a girl and a boy The girl had a poor mentality with a slightly positive C.S.F at 4½ years of age and the boy was mongoloid in type when young He defaulted at the age of 3½ so his subsequent history is not available.

These 4 cases, 2 mongols and 2 mongoloid type out of a total of about one thousand cases of congenital syphilis, do not appear to possess any statistical value in determining the aetiology of the condition. It must be mentioned, however that we did not have the opportunity of seeing all the children in the syphilitic families so that there may have been one or more mongols among the offspring of the syphilitic parents in my series. It is to be regretted that Benda did not examine his patients for syphilis, and the search for evidence of syphilis in the parents and other members of the families of mongols, as was carried out by Fraser and Watson, is clearly indicated.

Treatment of neurosyphilis

Whether the neurosyphilis were latent or manifest, treatment was always started with injections of arsenic together with mercury by mouth or with bismuth injections, and the fact that the spinal fluid was positive made us insist upon the patient being brought regularly for treatment. After the completion of a course followed by a month's rest the patient was seen again and the blood and spinal fluid retested. As a rule, and particularly in the younger children, an improvement would be manifest after one course of treatment. On the other hand in older children it

might be necessary to repeat the course and after another month a rest to retest the blood and spinal fluid. Usually after two or three such courses of treatment very considerable improvement would be manifest in both fluids: if so, the treatment would be continued on the same lines until the blood and spinal fluid had become negative. If such were the case the courses of injections would be continued, possibly varying the arsenical preparation or perhaps leaving out the arsenic and giving longer courses of bismuth, for at least another 12 months, examining the blood every 3 months and the spinal fluid at 6-monthly intervals. Then if both blood and C S F remained negative the child would be carefully followed up with a blood test every 3 months and a spinal fluid test every 6 months during the succeeding year. The usual annual overhaul would be carried out for as long as possible, with a blood test and clinical examination, and at the earliest sign of any return of neurological manifestations the spinal fluid would be retested.

Should a year's treatment on the lines indicated not show a manifest improvement in the C S F, a change-over was made in the drugs used. We tried neo-silver salvarsan and later tryparsamide and found the latter of considerable value. It is a pentavalent arsenical, readily soluble in water, and can be given by intravenous, intramuscular or deep subcutaneous injection, so that it can be used in children in whom the veins may be too small for intravenous medication. We often used it with bisoxyl mixed in the same syringe for deep subcutaneous or intramuscular injection with marked benefit to the patient. If after two years' treatment neurosyphilis was still active, malaria and intracisternal injections of salvarsanized serum, either alone or in combination, were given. 26 of our patients were treated with malaria and 12 with intracisternal injections. Several of the patients so treated did not do well eventually, and even though their neurosyphilis may have been rendered quiescent some of the patients died in institutions from remote effects such as tuberculosis or fits, the latter usually being called "epileptic." It remains to be seen if the introduction of penicillin in prophylaxis and treatment will prevent the occurrence of serious cases of neurosyphilis. Adequate records have not yet been published.

As the results of our observations have not been put on record a few relevant details may not be out of place. Of the 26 patients given malaria, 21 were treated at Great Ormond Street, the other 5 being too old or otherwise unsuitable for the hospital. The ages ranged from 3 8/12 years to 12 2/12 years. In 10 patients the malaria was mosquito-induced (1 to 8 mosquitoes fed). In 11 subcutaneous injections of malarial blood (1.5 to 4 ml.) were given. The incubation period was 11 to 15 days—average 13—in the mosquito group of patients, and 4 to 15 days—average 8—in the other group. The temperature sometimes exceeded 106° F., but actual rigors were the exception rather than the rule. Patients were usually allowed to have 10 "spikes" of temperature, after which the infection was cut short with *euquinine* (2 gr. = 120 mg., 3 times a day for 5 days).

Two patients had a relapse of malaria after an interval of 7 months. A few patients had 2 courses of malaria, one patient even a third course

There are obvious drawbacks to malaria therapy—the difficulty of obtaining infected blood or mosquitoes, the anaemia malaria produces, and the possibility of spreading the infection or of relapses occurring in the patient—so other forms of pyretotherapy have been recommended. Daily intravenous injections of T.A.B vaccine—starting with 50 million bacilli then giving 100 200 300 500 750 1 000 1 500 2 000 and 3 000 millions —were tried and can be recommended except in cases where the veins are likely to prove difficult to inject. Sulfosin was tried in a few cases but found to be unreliable in children. The Kettering hypertherm is a useful apparatus for raising a patient s temperature, but it has little vogue in this country

The other special form of treatment which we used for persistent neurosyphilis was the intracisternal injection of salvarsanized serum. This method was first advocated in this country by Sir James Purves Stewart, who introduced the method to my notice and treated one of my patients in this way He was an adult general paralytic to whom we gave malarial treatment and a course of intracisternal injections. His blood and spinal fluid became quite negative and the patient survived for over 20 years. In all, I treated 12 neurosyphilitic children by this method with only one disaster In that patient there was some difficulty in obtaining blood on the fifth occasion that the treatment was to be given with the result that the blood became infected with a haemolytic streptococcus. At that time it was not our practice to heat the serum to 56 C because it was thought some constituent of the blood might possibly be destroyed in this way so the blood and serum were obtained with aseptic precautions On this particular occasion, however the asepsis broke down and the serum injected into the child s cisterna gave rise to a streptococcal meningitis with fatal results. Since then we always heated the serum to 56 C. for an hour The accident happened in the pre prontosil and pre penicillin days.

Intracisternal puncture is now quite a common procedure, so one need not describe the operative technique in detail, but mention may be made of a simple contrivance we used for measuring the amount of C.S F withdrawn (shown me by Purves-Stewart) namely the barrel of a 10-ml. glass syringe fitted on to one end of a piece of rubber tubing about a yard long and attached at the other end to the cistern puncture needle. The needle having been duly inserted, the barrel of the syringe was held well below the level of the patient and the fluid, when it reached the 10-ml mark made more visible with a blue wax pencil, was tipped into a receptacle and the barrel allowed to fill again. In this way 30 or 40 ml. of spinal fluid could be safely withdrawn from the patient, and directly this had been done the diluted salvarsanized serum (equal parts of the serum and sterile

saline, warmed to about the body temperature) would be poured into the barrel, which would then be held up 2 to 3 feet above the patient. An *amount of diluted serum equivalent to the* amount of C.S F withdrawn would in this way be run into the spinal canal. At first the injections were given at fortnightly intervals, but afterwards a course of 6 injections was given at weekly *intervals which the patients tolerated quite well so well* in fact that they were able to get up the next day and play in the garden with the other children. The improvement in the spinal fluid which was examined weekly was in some cases remarkable and *I feel convinced* that this form of treatment is a valuable one which should be employed more frequently than it is. The reason why it is not more used no doubt is that it entails a considerable trouble in the preparation of the salvarsan ized serum, and there is a certain amount of diffidence about performing cisternal puncture.

The advent of penicillin has perhaps rendered many of these thera peutic measures more or less obsolete, because most cases of neurosyphilis would be treated at the outset with penicillin alone. I think it is still too early to speak about the ultimate result of penicillin therapy and certainly in this country it is generally held that penicillin should be supplemented by treatment with arsenic and/or bismuth.

Of the many cases of congenital neurosyphilis encountered a consider able number seemed to respond to the treatment above outlined, and by and large it appeared that the outlook for the patient was promising in the cases recognized and treated in early life. If neurosyphilis is not treated *within the first 5 years of life the condition doubtless on account of the* associated meningovascular lesions, will progress and affect adversely the parenchymatous tissues of the brain and spinal cord. Should the patient, *however* not be seen until after *5* years of age and have either a hemiplegia or suffer from fits and be mentally backward, particularly if the C S F should show a positive W R. and a paretic type of Lange curve, the outlook for the patient is gloomy indeed. No line of treatment whether it be malaria, intracisternal injections of salvarsanized serum arsphenamine mapharside tryparsamide bismuth or even I venture to believe penicillin itself will succeed in arresting the downward trend of the disease It is true that occasionally the patient may be cured of his syphilis, and even of his neurosyphilis, but as in the case of the girl F K who started her G P I at the age of 6 years and has survived to the age of 33 with a mental condition then where it was when *her active neuro-syphilis* started, one cannot hope that the scar tissue in the brain will ever take on the higher intellectual functions. It seems to be obvious, there fore, that *neurosyphilis must be anticipated rather than attempts be made* to cure it and this can only be done as has already been stated several times, by an early investigation of the C S F and if it be found positive by energetic *treatment* to render it permanently negative as early as

possible. The only exception to this generalization (as mentioned on p 312) is juvenile G.P.I. in a previously normal patient in whom the symptoms of G.P.I. come on in early adult life. Some of these patients may do moderately well.

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AFFECTIONS OF THE EYES

The eye is frequently affected in congenital syphilis indeed the commonest manifestation in the late form of the disease is interstitial keratitis. *It is almost pathognomonic of congenital syphilis, and as the remains of* this eye lesion may often be detected throughout life it is an important stigma which may be helpful when endeavouring to detect a case of third generation syphilis

In addition to the cornea practically all the anatomical structures of the eyeball may be affected by the disease and the lesions produced may result in complete blindness in a considerable number of patients. In the past blindness due to syphilis and gonococcal infections was a great social evil *but with the advance of knowledge and the consequent reduction in the* incidence of these diseases, a considerable improvement in the incidence of blindness has followed

Specific conjunctivitis, analogous to rhinitis is stated to occur in syphilitic infants, but in the few cases of redness and watering of the eyes we came across in our clinic no evidence of specific causation was discovered. The lacrimal apparatus is not infrequently affected in congenital syphilitics

in fact it has been stated by McLeod and Lemoine that excluding infections of the lacrimal sac, secondary to congenital occlusion of Hasner's valve, syphilis is by far the commonest cause of dacryocystitis in children. We had at least 4 such cases in our series. The patients usually have epiphora, the discharge becoming mucoid and occasionally actually purulent. The lacrimal gland itself is rarely affected by syphilitic inflammation

Interstitial Keratitis

The earliest description of the condition was accurately given by Mackenzie in 1840 The clinical manifestations, the corneal and scleral injection, the ground-glass appearance of the cornea, the age of onset the deafness and the nodes on the tibiae, all of which he noted, point to the fact that he was describing the condition we now call interstitial keratitis of syphilitic aetiology Mackenzie did not suggest syphilis as the cause or even as a cause of the condition which he called *scrofulous corneitis* It was Jonathan Hutchinson who, with his keen clinical acumen, recognized the connection between the ocular and associated manifestations, and in his classical memoir (1863) pinned down congenital syphilis as the most likely cause. Interstitial keratitis, the pegged central incisor teeth and nerve deafness constituted his well known triad, and since that time interstitial keratitis has become recognized as being the most frequent manifestation of late congenital syphilis. Its incidence is usually given as being between 30 and 50 per cent of all congenital syphilitic patients over the age of 2 years.

Table 20 gives the incidence of interstitial keratitis in patients over the age of 2 years, and, as will be noted, most observers record a marked preponderance of females over males It is difficult to explain why some observers, such as the Co-operative Clinical Group in the U S.A. failed to note any difference between the sexes, while Carvill and Derby also in the U S.A. found the usual proportion of about 40 males to 60 females. Likewise Igersheimer (1927), in Germany found the sexes equally affected, whereas British and French authorities found females to preponderate. Terrien (1933) states that over the age of 20 years the sexes are equally affected, so the ratio between the number of males to females will depend upon the type of clientèle whether from an adult or paediatric clinic or hospital.

Age at onset. It is said that interstitial keratitis may be present at birth or may develop shortly after birth we did not meet with such precocious cases Eight of the youngest patients in our series, 3 males and 5 females were between 2 and 3 years of age when the interstitial keratitis occurred. The highest incidence rate of interstitial keratitis is variously stated to occur between the ages of 6 or 7 and 14 or 15 years In our series it was at a lower level between 5 and 10 years of age doubtless

TABLE 20

Giving the Incidence and Sex Ratio of Interstitial Keratitis in Congenital Syphilis Patients over 2 years old from Various Sources

Observer	No of C.S. patients over 2	I.K.	%	Ratio M F
1 J Hutchinson, 1863	—	102	—	37 : 63
2. A. Fournier 1886	212	88	41.5	45 55
3 Stephenson, 1909	—	97	—	38 62
4. Holmes Spicer 1924	—	556	—	39 61
5 Carvill and Derby 1925	—	322	—	39 : 61
6. Jeans and Cooke 1930	707	195	27.5	Not stated.
7 Terrien, 1923	—	510	—	35 65
8 Co-operative Clinical Group 1937	1 010	403	39.9	No sex difference."
9. Nabarro (this series)	465	189[1]	40.6	35 65

[1] This number includes 9 patients (all females), 4 of whom had anterior ocular lesions such as mainly iritis with little keratitis, and 5 patients with rarer forms of keratitis referred to in the text.

reflecting the fact that our patients were drawn mainly from a children's hospital where the age limit for admission is 12 years. We had little opportunity of studying interstitial keratitis in adults except in the case of our own patients when adolescent or of their relatives. On the other hand writers who derive their figures from attendances at eye hospitals as opposed to the eye department of a children's hospital will obtain a higher range for the age at onset (see Fig 89)

Interstitial keratitis is essentially a disease of childhood and adolescence and is rare in adults, but an untreated congenital syphilitic is constantly at risk of interstitial keratitis up to 20 or 25 years of age, and patients even in the fourth or fifth decade may acquire the syndrome for the first time

Clinical description. For the clinical description I think the classical account given by Jonathan Hutchinson in 1863 in which he recorded the results of his years of observation cannot be much improved upon so with the added historical interest this account furnishes I reproduce Hutchinson's original description[1]

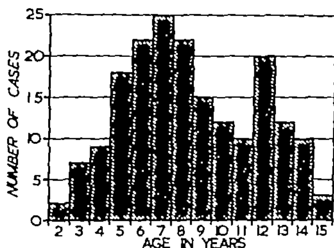
Chronic interstitial keratitis usually commences as a diffuse haziness near the centre of the cornea of one eye. There is at this stage no ulceration and exceedingly slight evidence of the congestion of any tunic. The patient however almost always complains of some irritability of the eye as well as of dim sight. If looked at carefully the dots of haze are seen to be in the structure of the cornea itself and not on either surface they are also separate from each other like so many microscopic masses of fog In the course of a few weeks, or it may be more rapidly the whole cornea, except

[1] I gratefully acknowledge the permission of Messrs J and A Churchill to reproduce.

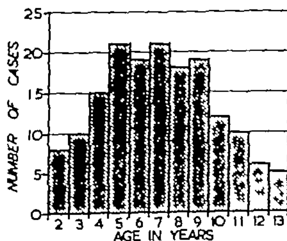
ing a band near its margin, has become densely opaque by the spreading and confluence of these interstitial opacities. Still, however the greater density of certain parts,—centres, as it were, of the disease,—is clearly perceptible. Early in this stage, the comparison to ground-glass is appropriate. There is now almost always a zone of sclerotic congestion and more or less intolerance of light with pains around the orbit. After from one to two months, the other cornea is attacked and goes through the same stages, but rather faster than the first. A period in which the patient is so far blind that there is but bare perception of light now often follows, after which the eye first affected begins to clear In the course of a year or eighteen months a very surprising degree of improvement has probably taken place. In milder cases, and under suitable treatment, the duration may be much less than this and the restoration to transparency complete, but in many instances patches of haze remain for years, if not for life. In the worst stage, the corneal surface looks slightly granular and from the very beginning it has lost its polish, and does not reflect images with definite outlines In certain cases after the ground-glass stage is passed, a yet more severe one ensues, in which the whole structure of the cornea becomes pink or salmon-coloured from vascularity and in these, crescentic fingers of vessels are often noticed at its circumference. In the best recoveries the eye usually remains somewhat damaged as to vision, and often a degree of abnormal expansion of the cornea is apparent. Only in one or two cases have I ever observed ulcers of distinguishable size on the surface of the cornea, and I have scarcely ever seen pustules on any part of it.

Lacrimation may occasionally be a marked feature of the condition. Photophobia may be so intense in these cases that the patient resorts to every expedient to avoid the light. On being led into the consulting room she hangs her head with the eyes turned away as far as possible from any source of light and keeps the eyelids tightly closed. It is often with the utmost difficulty that a glimpse of the corneae can be obtained For some months after the inflammation has subsided patients often tend to frown as if to avoid the light and in several instances this sign has suggested an inquiry into recent eye trouble.

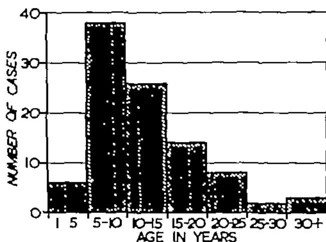
Uni or bilaterality In his original description Hutchinson, states that after one to two months the second eye is attacked. From this subsequent writers have concluded that the second eye is practically always affected so much so that when the second eye has not become affected the diagnosis of interstitial keratitis in the first eye has been doubted even by an ophthalmological colleague. Actually Hutchinson in his memoir reported bilateral interstitial keratitis in 91 of his 102 cases (89 per cent) The proneness of the second eye to become involved may undoubtedly be reduced by early and energetic treatment begun during the first 6 months of the original attack. The American Co-operative Clinical Group reported that under these conditions 39 out of 55 cases (71 per cent)



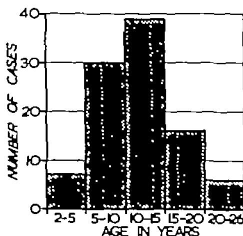
(a) Jeans and Cooke's series of cases—mainly a paediatric clinic



(b) Nabarro's series—mainly a paediatric clinic



(c) Stephenson's series mainly a paediatric clinic



(d) Hutchinson's series a "mixed" clinic

FIG. 89. Illustrating the difference in the age at onset of interstitial keratitis in mainly paediatric clinics (a–c) and mixed adult and children clinic (d)

remained unilateral Asmnder (1942) found that in 43 per cent of his cases the keratitis was limited to one eye, which happy result he attributed to the treatment adopted by him. Among our own series of 189 cases one eye only was affected in 42 or 22 per cent it must be remembered, however that our series includes a considerable number of patients who were treated in the ophthalmic department of our own hospital with the time-honoured mercury combined with atropine or even with mydriatics alone, and it was only after many months of such ineffectual treatment that it was suggested that injections of 606 might be tried. It would have been of interest had I been able to follow up the patients treated by us for congenital syphilis in infancy and early childhood, in order to ascertain the percentage who had developed keratitis Unfortunately this has not been practicable owing to the evacuation of so many of London s inhabitants during the war years. It is quite possible that the adequate treatment of the disease in infancy together with an annual overhaul, including a blood test may in the future be found to have been a valuable insurance against interstitial keratitis, as well as against the other manifestations of late congenital syphilis. The interval between the involvement of the two eyes may in the absence of antispecific treatment, vary from a few days to a few months, and in exceptional cases it may possibly extend to years. In our patients who were receiving treatment either for interstitial keratitis in one eye or for some other manifestation of late congenital syphilis such as Clutton s joints or periostitis of tibia, the records show that 14 out of 19 had involvement of the second eye within three months of the first eye being attacked. In the numerous other cases in which the interval was not specified or recorded it was probably short, and not more than 1 to 2 months. In 5 cases the interval between the involvement of the two eyes was longer than 6 months, namely 9 months, 1 year $1^{8}/_{12}$ $4^{10}/_{12}$ and $5\frac{1}{2}$ years respectively The first two were receiving treatment at the time whereas the last three had previously been given adequate treatment for their congenital syphilis It is perhaps worth recording that the two longest intervals, $4^{10}/_{12}$ and $5\frac{1}{2}$ years occurred in patients (1 male 1 female) both of whom were Wassermann-fast in the blood and likewise suffered from neurosyphilis. The American Clinical Group found that if the original attack of interstitial keratitis was adequately treated during the first 6 months, it was reasonably safe to assume after 2 years had elapsed that extension to the second eye would not occur Their results confirmed those of Carvill and Derby (1925) who stated that intensive treatment of interstitial keratitis in one eye may have some influence in preventing the involvement of the other eye

The teeth in interstitial keratitis

The characteristic notched and pegged upper central incisor teeth are the second component of the Hutchinsonian triad. Hutchinson s original

view (1863) that one never sees typical interstitial keratitis in both eyes without the characteristic test teeth has survived in some quarters even to this day although numerous observers have shown that it is no longer correct and, indeed, as has been pointed out in the account of the teeth (p 156) typical Hutchinsonian teeth are much less often seen in con genital syphilis to-day than they presumably were formerly

TABLE 21

Showing the State of the Teeth in 46 Patients with typical Interstitial Keratitis of Both Eyes

(a) *Incisors*		(b) *Molars*	
1 Typical Hutchinsonian (H³)	7	All 4 "Moon's"	29
2. Barrel or chisel-shaped (H²)	36	2. 1 or more "Moon"	12
3. Less marked than 2 or "Suggestive" (H¹)	43	3. Mulberry	3
4. tooth only affected	4	4. Crateriform decay	
5. Lower incisors small and spaced	15	5. Suggestive	4
6. Normal	51	6. Extracted	2
		7 Normal	62

It is seen from Table 21 (1) that by no means all, and not even the majority of the patients with interstitial keratitis have Hutchinsonian teeth (2) that nearly one half the patients had good incisors and molars and lastly (which is not shown in the table) that patients with interstitial keratitis in one eye only and a few even without ever having had interstitial keratitis had typical Hutchinsonian teeth.

Deafness in interstitial keratitis. Deafness was the third component of Hutchinson's triad, but this disability as a symptom of late congenital syphilis has also diminished during the past 25 years coincidently with the disease itself and doubtless as a result of the same cause—the better prophylaxis and early treatment of the disease. The total number of cases we encountered among our interstitial keratitis patients was 37 (9 male, 28 female), or 19·5 per cent. Not all of these were cases of inner-ear deafness, probably not more than one half some were undoubtedly due to middle-ear catarrh and in a few of these the deafness was only temporary

Arthritis periostitis and pharyngeal ulceration antecedent to or succeeding interstitial keratitis

One or occasionally two of these manifestations of late congenital syphilis may occur in association with interstitial keratitis although each of them may occur independently of the other The arthritis is usually of the Clutton type the periostitis usually affects the tibia and the pharyngeal ulceration often leads to necrosis with scarring of the nasopharynx, loss of uvula and perforation of the palate, as has previously been described (see p 138).

We encountered, in all, 61 joint cases among 338 congenital syphilis

patients with active lesions over the age of 2 years (18 per cent) Of these, 44 were simple Cluttons or Clutton types with complications such as periostitis of adjacent bones, while 17 were other types of joint lesions (see p 228), a *few of which might have been due to a cause unrelated to the* congenital syphilis.

Tables 22 and 23 show the incidence of each of these manifestations in congenital syphilis patients over 2 years of age and their relation to the incidence of interstitial keratitis in these patients.

TABLE 22

The Incidence of Clutton's Joints, Periostitis and Pharyngeal Ulceration among 338 Congenital Syphilis Patients over 2 years of age with Active Lesions and their Relation to Interstitial Keratitis in 189 Patients

C.S. patients over 2 years with active lesions		*Clutton joints*		*Periostitis*		*Ulceration of pharynx*	
With I.K.	189	28	14·8	23	8·1	14	7·3
Without I.K.	149	6	0·7	26	17·4	10	6·7
Total	338	44		49		24	

TABLE 23

The Time-relation of the Onset of Interstitial Keratitis to those of Clutton Joints, Periostitis and Ulceration of Pharynx in 65 Congenital Syphilis Patients over 2 years of age

Time relation		*Clutton joints*	*Periostitis*	*Ulceration of pharynx*
Before the I.K.		1	14	0
At the same time		3	1	2
After the I.K.		14	8	5
Uncertain		—	—	6 (see later)
Total	65	18	23	4

In Table 23 it is seen that when interstitial keratitis and Clutton's joints occur in the same patient, one half the patients develop the joint lesions *after the interstitial keratitis.* Of the 14, 5 had an interval of 1 month between the 2 lesions while in 12 of the cases the interval was 1 year or less. In one patient a period of $4^{8}/_{12}$ years elapsed between the interstitial keratitis and the Clutton's joints, and in the remaining case the interval was unspecified, the date of the *interstitial keratitis being unrecorded* In the case of the 11 patients in whom Clutton's joints preceded the interstitial keratitis the intervals ranged from 1 month to 15 months the two longest

being 12 and 15 months respectively Klauder (1951) stated that in his experience the occurrence of Clutton's joints *invariably* preceded that of interstitial keratitis, which, as Table 23 shows, was not our experience.

Almost twice as many cases of periostitis preceded the interstitial keratitis as came after it the intervals were as short as 1 month in the before and after and the limits were about 2½ years in both groups The only exception was a congenital mother who developed severe iritis and irido-cyclitis after the birth of her child, many years after she had suffered from periostitis. The gummatous ulceration of the pharynx cases are much more difficult to date since the disease so often starts insidiously runs a practically symptomless course, and when the patient is first seen with interstitial keratitis the varied signs of a former pharyngeal ulceration or active nasopharyngeal disease may be evident.

The teeth in manifestations of late active congenital syphilis

Hutchinson stated that patients with active ulceration of the nasopharynx or with evidence of former ulceration in the form of nasopharyngeal scarring, absence of uvula, etc. usually had perfectly normal teeth and only rarely were the typical Hutchinsonian teeth present. Our own observations did not entirely bear out Hutchinson's conclusions, as will be seen from Table 24 which shows that in 24 cases of pharyngeal ulceration Hutchinson and Moon teeth were found in 4 and that minor degrees of Hutchinson and Moon characteristics were seen in 11 further cases. In only 8 patients, one third of the number investigated, were the teeth normal.

The W.R. in the blood and C.S.F in cases of interstitial keratitis

Of the various manifestations of late congenital syphilis, interstitial keratitis and parenchymatous neurosyphilis are the most resistant to treatment if judged by the reversal of the blood W R. to a permanent negative On the other hand, a significant number of the patients who develop interstitial keratitis may have a negative or nearly negative blood reaction. We found that many patients especially those who were not treated with arsenicals and heavy metals during the acute state of the keratitis took much longer to acquire a negative S W R. than any other type of congenital syphilis patient. An analysis of our cases is shown in Table 25 It is seen that in group (3), 36 patients took more than 5 years to become serologically negative (one took as long as 23 years) and if this number be added to the 28 who were still strongly positive at the end of treatment, 64 of the 152 patients available for the analysis (42 per cent) may fairly be regarded as W R resistant It was frequently noted that in patients who took several years for the blood to reverse nearly to negative the final stages of the reversal to a clear negative occupied 12 or 18 months. Even

TABLE 24

Types of Teeth seen in Congenital Syphilis Patients with Clutton's Joints, Periostitis and Pharyngeal Ulceration alone and each in association with Interstitial Keratitis

Type of Teeth	*Clutton with I.K.*	*Clutton alone*	*Total*	*Periostitis with I.K.*	*Periostitis alone*	*Total*	*Pharyngeal ulceration with I.K.*	*Pharyngeal ulceration alone*	*Total*
H^1 and Moon molars	3	0	3	2	4	6	3	1	4
H^2 and Moon molars	5	1	6	1	0	1	1	0	1
Mild Degrees of H and Moon, including suggestive teeth	8	9	17	5	4	9	5	5	10
No record	3	3	6		4	5	0	1	1
Teeth good	9	3	2	14	14	28	5	3	8
Totals	28	6	44	23	26	49	14	10	24

Note: Where there was no record the teeth were almost certainly *not* characteristic H^2 or H^3 incisors.

TABLE 25

Serum Wassermann Reaction in 89 Cases of Interstitial Keratitis

S.W.R. at onset of the I.K.	*S.W.R. at last investigation*	*Number*	% (52 cases)
(1) Negative or nearly so	Negative.	13	9·8
(2) *Positive*	*Positive.*	28	18·4
(3) Positive	Negative in 5 years or less.	73	48
	Negative or nearly so, in more than 5 years.	36	23·6
	Total	152	
	Cases in which insufficient data	37	
	Total	189	

then some of them relapsed again after a few months before becoming finally negative. It has long appeared to me to be of doubtful value to worry about Wassermann fastness in a patient, provided he or she has received the recognized sufficiency of treatment for the clinical condition. In several cases we found that the W.R. became negative in course of time without any further treatment being given. Although so many of our interstitial keratitis patients were W.R. resistant several of the most acute and persistent cases were not W.R. resistant or W.R. fast. We had one girl who had been nearly blind since the age of 5 years from continuous attacks of interstitial keratitis, who when she came under our care for a fresh attack at the age of 11 had a negative W.R. in blood and cerebro-spinal fluid the S.W.R. remaining persistently negative during the 5 subsequent years of treatment. Two other patients who had severe attacks of interstitial keratitis, with one and three relapses respectively had serological reactions which were not correspondingly resistant, for in both cases reversal was achieved at the end of 2 years treatment. The details of these three patients are as follows

H.L., who had been under our care since he was 8 years old, had I.K. in the left eye only at the age of 5½ years, for which he was treated, but without injections, at another hospital. When he attended Great Ormond Street he had active ulceration of the palate, and the left eye showed scars of the old I.K. After 2 years treatment with arsenicals and heavy metal, supplemented by thyroid extract, the ulceration of the palate healed, leaving a small hole in the roof of the mouth, and deafness was coming on at 9½ years. At the age of 19 there was a relapse of the I.K. due, the patient thought, to grit from a steam engine blowing into the eye. Our ophthalmic colleague regarded it as a "flare-up of the old I.K." (14 years previously) and as being "not now specific." His W.R. was then negative and the patient was given no antispecific treatment. He remained fairly well, his hearing having recovered. He married at the age of 24, and 2

years later a crumb of bread in the eye is said to have damaged the cornea. The eye became very inflamed the condition being diagnosed by another ophthalmic colleague as I K. with keratic precipitates." The W R., which had once been negative at the age of 18½ was now slightly positive. The condition subsided with mydriatic ointment. This patient had two relapses of I K 14 and 21 years after the original acute attack and on each occasion the relapse appears to have been caused by the trauma due to a foreign body in the eye

Another patient, a girl aged 11²/₁₂ years, developed I K in both eyes after having received a course of 10 bismostab injections (12·25 ml.) Although she was given another course of 14 bismostab injections and subsequently 26 injections of stabilarsan mercury iodide and later potassium iodide she had three attacks of I K in the first 12 months, the first two in both eyes, the third in the left eye only About 20 months after the commencement of the original attack, a series of three relapses occurred during the ensuing 10 months, both eyes being affected in the first of these relapses and the right eye in the two last. When the patient defaulted at 14¹/₁₂ years there was a little conjunctival injection with slight corneal scarring

Another patient also a girl aged 11²/₁₂ years when she came to our clinic gave the following history In infancy she had a rash no snuffles or epiphysitis. At the age of 5 years she developed I K., for which she was treated with mercury at an eye hospital but the attacks of keratitis were almost continuous. When we saw her she was nearly blind from I K and iritis there was intense photophobia and marked lacrimation The teeth showed Hutchinson and Moon characteristics. The S W R. was negative and the C S F was normal in all respects. In view of the unusual history she was treated with injections of neo-silver-salvarsan combined with hydrarg perchlor and potassium iodide orally during the first course. During the second to the sixth courses of silver-salvarsan she was given mercury iodide and afterwards tiodine [1] The eyes improved so that the patient was able to read, but the corneal opacity was still marked. She was later treated by diathermy and the mercury vapour lamp with but little benefit to her eyes or vision. Unfortunately fever therapy was not at that time (1928) a recognized mode of treatment for chronic I K and the patient's condition was deteriorating when she was lost sight of

The U S A Co-operative Clinical Group found that in congenital syphilis patients with acute lesions and a fixed W R. [2] satisfactory clinical results were obtained in 51 per cent of the cases and 12 per cent progressed or relapsed whereas of the patients whose W R. was not fixed, 64 per cent responded well and only 7 per cent showed progression of the lesion or relapse

[1] Tiodine is a brand of thiosinamine ethyl iodide made by Cognet of Paris London agent, Roberts and Co New Bond Street London W 1 It is usually given either in pills (50 mg 2 to 5 daily with meal) or by subcutaneous or intramuscular injection, every other day Proportionately less for children Tiodine is indicated for the absorption of fibrous tissue Thiosinamine is mentioned in B.P C 1949 p 911

[2] Cases in which the blood serological reaction was persistently positive over a period of 2 years or more were considered as fast by the American investigators but their account does not make it clear whether a blood of diminishing titre but still positive at the end of 2 years would be considered "fast

Interstitial keratitis and neurosyphilis

There are few references in the literature to the relation between interstitial keratitis and congenital neurosyphilis. In Jeans and Cooke's series of 228 children with neurosyphilis (the age group was not stated) 123 had latent neurosyphilis and 105 clinical neurosyphilis of the former 14 had active keratitis (11 4 per cent) whereas of the latter only 2 had keratitis and another patient had a history of keratitis (2 8 per cent) It would appear therefore, that the conditions interstitial keratitis and clinical neurosyphilis are only rarely found associated in the same patient, whereas latent neurosyphilis in association with interstitial keratitis is four times as common. Viewed from a different angle our results show a similar trend. We examined the C S.F in 127 patients with interstitial keratitis with the results shown in Table 26

TABLE 26

The Results of the C.S.F Investigation in 127 Patients over 2 years old with I terstitial Keratitis with reference to Latent and Clinical Neurosyphilis

No clinical evidence of neurosyphilis when first seen	2		
Clinical evidence of neurosyphilis	6		
	—		Total 27
C.S.F negative			
(a) before treatment	48		
(b) after treatment, much or some	64[1]		
	—	2	
C.S F positive			
(a) with latent neurosyphilis	9		
(b) with clinical neurosyphilis	6		
	—	5	
		—	Total 27

Of the 15 patients with positive C.S F
(a) 8 became negative—6 latent,[2] 2 clinical [3] neurosyphilitics.
(b) 7 were W.R. fast—3 latent, 4 clinical [3] neurosyphilitics.

[1] Some of these patients would undoubtedly have been found positive had their C.S.F been examined before treatment was started

[2] The patients in this category became negative after the following periods $^{6}/_{12}$, $^{8}/_{12}$ ( ), $1^{2}/_{12}$ and $2^{3}/_{12}$ years. One was positive at 10, 2 and 5 years of age but negative when examined at 22 years.

[3] One patient had positive fluid when examined at 6 years but it was negativ on re-examination at years, after which he defaulted. The other patient in this category became negative in the C.S.F in 6 months, and was still alive in 950 and doing useful work in the ward of an institution of which he was an inmate at the age of 29 years.

A brother and sister were in this category the boy had positive blood and C.S.F after 6 years treatment, which included malaria shortly before he defaulted. The girl had positive blood during $4\frac{1}{2}$ years and positiv C.S.F at /12 and $1\ ^{4}/_{12}$ years. The treatment she received was not so intensive as the brother s.

This category includes a boy who died of juvenile paresis at the age of $13^{10}/_{12}$ years. The other 6 W.R.-fast patients were unfortunately lost sight of and their fate is unknown.

The table shows that at least 6 patients with clinical and at least 9 with latent neurosyphilis developed interstitial keratitis. The Co-operative Clinical Group (1937) in their series of 1,010 cases of late congenital syphilis recorded interstitial keratitis in 33 per cent and neurosyphilis in about 10 per cent, but they made no mention of the incidence of interstitial

keratitis in the total number compared with that in the patients with neurosyphilis, nor did they state whether the cerebrospinal fluid W. R. was fixed or reversible.

An account of the histology and pathology of the syndrome can be obtained from any good textbook on ophthalmology but mention may be made of the sequelae we noted in our patients. Several of them had repeated attacks of conjunctivitis, with redness and lacrimation, after the interstitial keratitis was apparently cured. These attacks did not require or respond to further antisyphilitic treatment if the patient had already been adequately treated and had a negative W. R. The next most common sequel was a moderate degree of myopia which several patients developed while two patients suffered respectively from bilateral retinal haemorrhages at 14 and 19 years (2 and 14 years respectively after the interstitial keratitis), and from detachment of the left retina at 16 years of age, 12 years after interstitial keratitis in both eyes. We had no case of glaucoma following interstitial keratitis.

The pathogenesis of interstitial keratitis has long been one of the problems of congenital syphilis. Whilst interstitial keratitis is the commonest condition met with in late congenital syphilis, it occurs but rarely in acquired syphilis. It starts in children between the ages of 5 and 15 and it is rare for it to start in adult life. Females are affected in preference to males. The therapeutics is paradoxical in its behaviour. Interstitial keratitis may make its first appearance while the patient is actually being treated for latent syphilis or some active manifestation of the disease. It responds slowly to treatment, especially if this be not intensive and adequate, so that many ophthalmologists during the second and third decades of this century were so sceptical as to the value of treatment with arsenicals and bismuth that the majority of them continued to resort to the time-honoured mercury and potassium iodide. Furthermore, no known method of treatment will with certainty prevent the condition occurring in the other eye or will with certainty prevent relapses or recurrences. In many cases the blood W. R. is either "fast" or takes a long time to reverse to negative; on the other hand an original attack or a relapse of interstitial keratitis may arise several years after adequate treatment has been given and possibly with negative serological reactions. It would be legitimate to assume from the foregoing observations that interstitial keratitis is not an ordinary organ or tissue infection with the treponema, but the precise mechanism of its production is still uncertain.

Let us consider briefly some anatomical and experimental data. Syphilitic foetuses and neonates show the treponema, often in large numbers, in many of the ocular structures, including the cornea and uvea, and it is noteworthy that the cornea may be quite clear and the uvea histologically normal in these cases, from which it may be concluded that the presence of treponemata in them cannot be the sole cause of interstitial keratitis.

It is possible that the treponemata present in such a clear cornea may survive, perhaps in a modified form such as a spore or virus body and subsequently give rise to interstitial keratitis when favourable conditions present themselves.

The earliest recorded experimental inoculations were those of Haensell (1881), who produced keratitis in rabbits by the injection of syphilitic material into their corneae. Not until 25 years later did Bertarelli (1906) repeat Haensell's observations, and he was able to demonstrate the newly discovered *T. pallidum* between the lamellae of the infected corneae. Since that time many investigators (Neisser 1906 Hoffmann and Bruening 1907 and others cited by Harrison 1931) extended the experimental investigations to other aspects of syphilis in animals.

Some time after the testicular inoculation of rabbits with syphilis, the animals develop a metastatic keratitis which histologically resembles human interstitial keratitis. The treponema may be found in the uninflamed parts of the cornea but not in the inflamed area in these cases. It is quite likely that a similar phenomenon occurs in the human eye and, as Igersheimer points out (1920, 1922, 1951), even if it be assumed that there are no treponemata in the cornea at the time of the keratitis, it is highly probable that they had been present previously living in harmony with the corneal tissues and without giving rise to any inflammatory reaction. During this temporary and apparently harmonious sojourn of the treponema in the corneal substance, the cornea presumably becomes sensitized, with the result that under favourable conditions interstitial keratitis may occur

It is possible that one or more of the suggested causes are factors in its production in different cases. For the reasons given above, the direct action of the treponema upon the corneal tissue is not the cause, otherwise during the treponaemia of acquired syphilis in adults interstitial keratitis should be common, whereas it is actually very rare and according to some it does not occur at all in the acquired adult disease. Why more than 95 per cent of the cases occur in children, adolescents and young adults and only 2 or 3 per cent in adult acquired syphilis can only be surmised. It seems to indicate that the *juvenile* corneal tissues are more vulnerable to this type of inflammation, and that juvenility is an almost indispensable factor in its causation.

Sensitization of the corneal tissues during their treponemal invasion in foetal and neonatal life so that they become more susceptible to toxins or other allergens brought to them from other foci in the body has been suggested as a likely cause. Igersheimer (1913 1920–2) and Loewenstein (1927) have investigated keratitis in experimental syphilis in rabbits and by the intracorneal injection of human serum were able to produce interstitial keratitis in the presumably sensitized corneae. Loewenstein concluded from his experiments that disturbances of nutrition, consequent

upon vascular changes in the anterior ciliary arteries play an important part in the causation of interstitial keratitis. Holmes Spicer (1924) expressed the opinion that interstitial keratitis is likely to occur only if the treponema is at a particular stage of evolution in the cornea. If the treponema be present but the required stage of evolution be not attained, there will be no attack if it be not attained in the two eyes simultaneously there will be an interval between the attacks in the two eyes. If the required state of evolution have been reached there will be an attack of interstitial keratitis in the absence of any stimulus and in spite of anything that one may do by way of prophylaxis.

Terrien (1933) wrote that Onfray in a thesis to the University of Paris in 1903 was the first to suggest hormonic dysfunction in interstitial keratitis, *and that he himself agreed with Onfray's thesis, for interstitial* keratitis occurs most frequently about the period of puberty. This latter assertion is not in agreement with our own experience for in our patients the highest incidence was between the ages of 5 and 10 years, and Stephenson obtained the same age incidence from his patients who like our own were derived mainly from a children's hospital. Klauder Gross and Hanno (1951) from their investigations into the relation of the endocrine glands to the pathogenesis of interstitial keratitis, came to the conclusion that such a relation exists. Evidence was obtained of hypothyroidism, suppression of androgenic function and other hormonal disturbances.

The part played by trauma in initiating an attack of interstitial keratitis has been long debated. Terrien, in 1911 summarized the 94 cases of alleged trauma reported in the literature up to that time and was of the opinion that hardly 12 of them were genuine. Most patients with acute eye trouble will probably recall an injury to the eye or that something had blown into it some time before the inflammation set in. It is important to inquire fully into the alleged incident, for it may eventually be discovered that the incident happened too long ago or too recently for it to have been the exciting cause. Quite often, however the patient's or the parents' *account may be accurate, and it is frequently observed how trivial the cause* may have been such as a minute foreign body in the eye, for such an intense inflammation to occur as may at times ensue. As McLeod and Lemoine state, figures vary widely from 1·7 per cent in 401 cases (Cunningham) to 18 per cent (Langendorff cited by Carvill and Derby). Our own figures are rather interesting 123 *females had primary attacks of* interstitial keratitis and 15 relapses making 138 attacks in all. There was a history of trauma in only 2 attacks (1·4 per cent) and one of these knocking the eye against a chair whilst dancing 6 months previously must be considered highly problematical as the exciting agent of the interstitial keratitis. The other case in which sand in the eyes was the alleged cause is much more plausible. Other exciting causes appeared to be acute specific fevers, 5 cases 3 original attacks were stated by the

mothers to have followed measles, and 1 relapse each to have occurred after chickenpox and german measles one original attack was attributed to an operation on the patient's leg 4½ months previously one attack (of disciform keratitis ') occurred with the onset of menstruation at $13^{10}/_{12}$ years and 3 or 4 congenitally-syphilitic mothers stated that their attacks originated in connection with the birth of their children. Sixty-six males had primary attacks and 9 relapses, making in all 75 attacks. There was a history of trauma in 6 of the primary attacks and in 3 of the relapses (12 per cent) One patient referred 2 relapses to traumata one at 19 he attributed to grit from a train blowing into the eye, and the second at 26 years of age, when the cornea was damaged by a bread-crumb flying into the eye (see p 339) One attack was attributed to an operation for tonsils and adenoids, and in 2 patients attacks followed whooping-cough and scarlet fever respectively It appears from our figures, small though they be, that males are more likely than females to be victims of foreign bodies in the eye, which makes the preponderance of females among sufferers of interstitial keratitis the more difficult to explain.

To sum up from the available evidence, clinical and experimental, the pathogenesis of interstitial keratitis would appear to be somewhat as follows. It is primarily though not directly due to the *T pallidum* which during foetal or neonatal life has inhabited and increased the sensitivity of the cornea without giving rise to any inflammatory reaction or any visible change of structure. The condition is commoner in girls than in boys and may be in some way sex linked. It is possible that endocrine dysfunction may play a part in its pathogenesis but it does not seem likely as has been suggested by some authors, that its onset is associated with the advent of puberty The exciting agent is undoubtedly a trauma to the eye in a varying proportion of the cases. Infectious disease, an operation pregnancy and childbirth and other agencies which tend to lower the general resistance may act as the exciting cause and lastly allergy by bringing to the sensitized cornea toxins or allergens from another part of the body and/or by reactivating dormant treponemata in the cornea may be an important cause.

Treatment of interstitial keratitis

All venereologists and most ophthalmic surgeons nowadays give early and energetic treatment to patients suffering from interstitial keratitis Many authorities have reported that the severity and duration of the original attack, unfortunate sequelae, and the liability of spread to the other eye and of relapses are all reduced by early intensive treatment Our own observations bear out these findings. The diagnosis should be confirmed by an ophthalmic surgeon and the treatment carried out by the venereologist jointly with his ophthalmological colleague, unless the venereologist in-charge has specialized knowledge of eye affections. As

has already been indicated, the eye lesions of congenital syphilis are highly *refractory to half hearted or mild treatment* so that prophylactic or anticipatory treatment at the earliest possible moment is desirable Most important of all is the prevention of congenital syphilis by the testing and—if necessary—the treatment of the mother in pregnancy Next in importance comes *the earliest possible efficient treatment* of the child to prevent the later manifestations—interstitial keratitis neurosyphilis and nerve deafness

The interstitial keratitis cases at Great Ormond Street who were referred to our clinic for treatment were given injections of neo-arsphenamines with mercury by mouth or alternating with injections of bismuth (bismuth metal or trépol and later bismuth oxychloride) and in some cases bismuth preparations alone. Many of the patients treated from 1920 onwards received, in addition oral treatment with thyroid extract. If the corneae cleared rather slowly potassium iodide gr 5–30 (0 3–1 8 G) or more, three times daily frequently appeared to promote resolution. One *of our patients, a congenital mother who was nearly blind at 44 from* corneal nebulae, showed a remarkable clearance of her corneae after extraction of several septic teeth. This may have been pure coincidence

During the acute state the pupil must be dilated and careful watch kept *on the eye that the pupil remains dilated to prevent the formation of* adhesions. It is necessary to mention that the atropin ointment used for this purpose must be applied to the *inside of* the lower lid and not be smeared on the outside of the lids as one of my nurses once did! If the eye is very painful at this stage it is usual to apply hot applications, though Assinder objected to their use and stated that by his method of treatment he succeeded in limiting the keratitis to one eye in 43 per cent of his cases

We found that no relation appeared to exist between the titre and the duration of the patient's blood Wassermann reaction and the clinical course of the interstitial keratitis, but our experience certainly revealed the fact that the interstitial keratitis was usually of a milder type if it occurred during treatment for active syphilis of some other part of the body or for latent syphilis, and or if treatment was started early within a month or two of the onset of the acute attack.

The modern treatment as outlined by Klauder Vandoren Cross, Hanno and others places fever therapy in the forefront of the scheme Malaria is not always necessary they say intravenous injections of typhoid or T.A B vaccine, every other day usually suffice. For mild cases 4 to 6 bouts of fever may suffice, *for moderate cases 8 fever spikes are recom*mended, and for severe cases 12 to 14 febrile attacks. During fever therapy treatment with penicillin or heavy metal is instituted Klauder's study (1947) having failed to demonstrate any superiority of penicillin over arsenic and bismuth therapy *The dose of penicillin recommended is*

2.4 mega units (either in aqueous or oily base) spread over about 12 days. The addition of gland therapy (dried thyroid gland) appeared to be of use in severe cases. The dose used was 2 or 3 grains (130–195 mg) daily for 2 to 4 weeks. The effects of A.C.T.H. and of cortisone were also tested. Patients with severe interstitial keratitis derived no benefit from either drug administered for 7 to 10 days, in contrast to similar severe cases which were benefited by 7 to 10 days of fever plus thyroid therapy. Mild and moderate cases were benefited to a variable degree; in some instances dramatic relief was afforded by local therapy with cortisone. This has also been reported by Horne (1951) and by Simpson, Rosenblum, Wood and Stammer (1951). To sum up, there is no doubt that in severe cases, where there is a likelihood of the lamellar structure of the cornea being damaged, approved methods of treatment, early and energetically applied, may yield surprisingly good results in the affected eye and may prevent involvement of the other eye.

Relapses in interstitial keratitis

Hutchinson in his original memoir stated that relapses of interstitial keratitis were "decidedly exceptional," but that he had a few instances of relapse. Modern authorities have been less fortunate in this respect. Carvill and Derby (1925) define a relapse as a "recurrence of the attack of inflammation one year or more after the subsidence of the acute symptoms of the primary attack of interstitial keratitis." The American Co-operative Group have accepted this definition and they found that of 149 early acute cases, 31 (21 per cent) had one or more relapses during observation or treatment. The best method of avoiding relapse, they say, is to give continuous adequate treatment while the patient is in the early acute stage. Fifteen per cent of the patients suffered a relapse, as contrasted with 29 per cent who received irregular treatment in the early stage. By adequate treatment they meant more than 15 injections of arsenicals with 31 or more injections (or weeks) of heavy-metal treatment. In the early acute stage they found it preferable not to give iodides or fever and foreign protein therapy, though these adjuncts to treatment are recommended in chronic or relapsing types of case. The summary and conclusions drawn from their survey by the Co-operative Group are as follows: (1) interstitial keratitis was found in about one third of the 1,010 cases of late congenital syphilis. (2) Early treatment held out greater promise of a satisfactory clinical outcome than did delay in the treatment until after the condition had become chronic or healed spontaneously leaving residual scars. (3) W.R. fastness in acute symptomatic congenital syphilis diminished a favourable prognosis, whereas in latent cases it seemed to have little bearing on the outcome. (4) Patients treated under 15 years of age responded more satisfactorily than did older patients. (5) Those treated adequately for more than a year had a greater number of good clinical

results (62 per cent) than patients treated for a shorter time (49 per cent) (6) A patient with congenital syphilis is continuously at risk of developing interstitial keratitis up to the age of 25 years unless given adequate anti syphilitic treatment. (7) The best prophylactic treatment for interstitial keratitis is the administration of adequate continuous therapy for all latent congenital syphilitic patients. They found that 36 per cent of untreated congenital syphilitics developed interstitial keratitis, in contrast with only 2 per cent of patients who had received modern antisyphilitic treatment. (8) Early adequate treatment of the interstitial keratitis at the time of involvement of the first eye (within the first 6 months) limited the inflam mation to that eye in 71 per cent of the cases. (9) All interstitial keratitis patients should be given adequate treatment as outlined above as it was found that six times as many untreated as treated patients lost useful vision. (10) In early acute cases adequate arsenical and heavy metal treat ment given continuously gave excellent results in 93 per cent of the cases. This survey was undertaken in the pre-penicillin era and there is no com parable survey since the introduction of penicillin for the treatment of syphilis. *Doubtless courses of penicillin, 2.4 mega-units, could satis-factorily* take the place of an equivalent course of arsenicals and heavy metal treatment. In this country most, if not all authorities prefer to give intermittent courses of arsenicals and heavy metal with monthly periods of rest to allow the excretory organs to recover *It is possible that* the ideal treatment is to give a course of penicillin during these rest periods.

Of our series of 189 cases of interstitial keratitis many must be left out of account as regards relapse since they attended eye hospitals where they frequently received no systematic antisyphilitic treatment. In our clinic we treated 115 cases of interstitial keratitis in children ranging from 2 to 12 years of age with relapses in 15 of the patients, a relapse rate of 13 per cent The interval between the original acute attack and the relapse varied from 1 1/12 up to as many as 14 and 21 years, and a congenital mother informed us that she had suffered two relapses 4 and 24 years respectively after the original acute attacks though we did not verify her statement We have already referred to a few of our patients in whom we observed two and three relapses, and in several cases relapses occurred when the blood W R had been negative for some time, even as long as 4 or 5 years.

As a rule relapses are milder and more amenable to treatment than are early acute attacks occasionally they may be severe.

Keratitis other than interstitial keratitis

Rare forms of keratitis occur some of them attributed to syphilis, a few of which we have encountered and which may have had a syphilitic aeti ology Two patients, girls of 3 and 4 7/12 years respectively were diagnosed by our ophthalmologist Doyne as suffering from keratitis punctata

profunda, the substance of the cornea being unaffected. This condition was recorded in congenital syphilis by Bryn in 1927 and is described by Duke-Elder A third case of the kind in a girl of $9^{10}/_{12}$ years (left eye only) after much treatment and occurring during a course of bismuth injections, our ophthalmologist described as being more of an iritis than a keratitis. The condition lasted on and off for a year

Another girl at the age of $13^{10}/_{12}$ when she had her first menstrual period became nebulous in the right eye only without any concomitant inflammation. It is possible that the infection in this patient had been acquired early in infancy Penman who was our ophthalmic surgeon at that time, reported the condition as being obviously of long standing not interstitial keratitis but disciform keratitis of the right eye. Duke Elder states that Verrey in 1935 described cases of this condition in syphilitic patients.

Another of our patients at the age of 26 and 20 years after her blood and C.S F had become negative as the result of intensive treatment, developed Keratitis linearis migrans, which cleared quickly and completely after a course of penicillin and bismoxyl though it is problematical that the aetiology was active syphilis. She had been amaurotic in the other eye for many years from macular choroiditis. Duke-Elder briefly refers to the condition, which was first described by A. Fuchs in 1926

The following case is of sufficient interest to be put on record. The patient, born in 1909 was a "healthy" baby and girl until her marriage at the age of 17 The following year during her puerperium after the birth of a healthy daughter she developed inflammation of the right eye which was diagnosed at an ophthalmic hospital as severe iritis, cyclitis and keratitis of tuberculous origin. There were new vessels on the iris and a slight subepithelial vascularization of the cornea at 6 o clock." She was then seen by a physician who was of the opinion that the condition was most likely due to uterine sepsis. After treatment on these lines, the eye cleared in a year the other eye remaining unaffected. No W R. was taken and the patient was not given antisyphilitic treatment. A second daughter born to the patient 7 years after the first child, had a rash on her face at the age of 4 weeks and no other symptoms suggestive of congenital syphilis when she was examined by us at the Children's Hospital. Her W R. was then negative while that of the mother (now aged 26) was strongly positive. The husband's blood was examined at the Maternity Hospital and found to give a negative W R., from which it was concluded that the mother was in all probability a congenital syphilitic. We examined her carefully from that point of view and found that she had a healthy facies and good teeth but there was a small yellow nodule (? a gumma) in the right pillar of the fauces which she said had been present for about 9 months without causing any inconvenience. She informed us that she had had a lump on her leg as long as she could remember An X ray examination at the age of 26 years revealed "Residual changes in the right tibia and old periostitis in the left femur The diagnosis of congenital syphilis appeared to be confirmed by these findings, but there remained the rather remote possibility as she was healthy at birth and afterwards that she might, at an early age have acquired syphilis from her mother The ophthalmic surgeon at the eye hospital she originally attended for her iritis,

etc., on being informed of our discovery of a positive W. R. in the patient's blood, said that "explained the whole thing, but it was unusual for the second eye to escape in the absence of antisyphilitic treatment. We treated her intensively with arsenicals and mercury and then with bismuth, yet with little effect on the W. R., and after about 18 months she complained of deafness. The C.S.F. examined about 4 months later was normal in all respects, nevertheless her blood remained strongly positive until she was 30, when the patient was apparently well when last seen. The throat showed a shallow "punched-out" crater in the right faucial pillar in the situation of the yellow nodule seen 4 years previously the right pupil was slightly bigger than the left, and both pupils reacted well to light and there was no Rombergism. The right tibia was still thickened The deafness had disappeared and there had been no return of the eye trouble. The Wassermann fastness pointed to congenital rather than acquired syphilis, despite the absence of infantile and childhood symptoms in the patient. Her mother's obstetric history was as follows

Married 1905

1 1906 M Not seen by us or tested.
2 1909 F Pt. Healthy infant and child. History recorded above.
3 ? SB. M
4. ? SB. F
5 ? M Lived one week.
6. 1920 M Healthy baby and child. Blood and C.S.F. negative at 18 years.
7 1922 M. Delicate baby Interstitial keratitis at 9 years. W.R. + + at 16 years. C.S.F. neg
8. 1929 M Born after mother's 6 injections during fifth and sixth months of pregnancy Not seen but said to be "jumpy" at 5 years of age.

As stated previously it is just possible that the mother was infected after the second child (our patient) was born and that our patient acquired the infection from her mother

Gargoylism is another cause of cloudy corneae which may be mistaken for the interstitial keratitis of congenital syphilis We saw such a case in the year 1917 who originally attended the Outpatients Department of the Children's Hospital under the care of Dr Poynton and Mr Addison at the age of 9 months on account of snuffles and possible spinal trouble Because of the snuffles and enlargement of the spleen congenital syphilis was suspected and the child was sent for a blood test. The W. R. was reported weakly positive in both mother and child the father's blood was negative On two subsequent occasions the mother's blood gave a negative W. R. but the child's blood on three separate occasions during the ensuing 12 months gave a weakly positive reaction (4.3.0.0.). Our ophthalmologist who saw the child at the age of 14 months noted a diffuse haze of the corneae surfaces bright and agreed with the physician's diagnosis of congenital syphilis. The patient was treated with mercury and later by arsphenamine injections but the eyes did not show any improvement with antisyphilitic treatment and the patient's general

condition remained about the same. At 2½ years he was operated on for double inguinal hernia. Shortly afterwards his head enlarged, and at the age of 4½ years he was dwarfed and manifestly mentally deficient. The patient was now seen by another physician, who thought his condition was cretinoid and treated him with thyroid. Finally at the age of 5½ years he was brought to the hospital cyanosed and obviously moribund, and with such a repellent appearance that he was, unfortunately, not photographed. Death occurred on the following day There is no doubt that this patient seen and treated between the years 1917 and 1922, and thought to be a congenital syphilitic, was a victim of the condition now called gargoylism.

This syndrome is thought to be due to disordered lipoid metabolism which conceivably might give rise to a false-positive W R. of varying intensity a weakly positive as in the case above recorded, or a strong positive as was found by the late Dr E. ff Creed in another case. This was the child who was case 3 in the series given by Ellis, Sheldon and Capon (1935) and had been diagnosed by her general practitioner as being a text book case of congenital syphilis with snuffles, chronic iritis en larged liver epiphysitis, etc. Creed found the W R. 200 units strong and as a result of vigorous treatment with mercury and bismuth the W R. was reversed to negative a year later Ten months afterwards when she was 4½ years old, I saw the child at the Children s Hospital, Great Ormond Street. We found her blood W R. negative but the Kahn positive her cerebrospinal fluid was quite normal.

I had previously in 1932, seen and studied with Poynton another patient (Miriam J case 2 in the series given by Ellis, Sheldon and Capon) The child was sent to Poynton for diagnosis and particularly for the elimina tion of congenital syphilis. The Wassermann and Kahn tests were negative, as were also tests for filariasis, malaria, Brucellosis, and intestinal ova and parasites.

These investigations were carried out as the child was born and had lived for 3 years in British Guiana. Poynton recognized that the syndrome exhibited by the patient—the grotesque appearance, with large head frontal bossing flattened nose, thick lips and hazy corneae, the hepato-splenomegaly mental deficiency and radiological changes in the bones—was something very unusual and hitherto undescribed. He told me that on one of his ward rounds he remarked that the child reminded him of the gargoyles one sees on old cathedrals. It was Ellis, Sheldon and Capon who subsequently gave the name Gargoylism to the syndrome.

Other causes of interstitial keratitis than congenital syphilis are (1) acquired syphilis in adults, in whom its occurrence is rare in the experi ence of some writers (Klauder 1951) (2) acquired syphilis in children which Jeans and Cooke mention and of which we have seen a few instances (3) tuberculosis is an undoubted cause of interstitial keratitis and it will be recalled that Mackenzie originally described the syphilitic variety as

scrofulous corneitis It is often difficult and sometimes impossible to differentiate the syphilitic from the tuberculous variety of interstitial keratitis and in rare cases the condition may be of combined aetiology Lastly cases like the following which are difficult to interpret

R.C. was born during the first world war and is said to have had snuffles shortly after birth. At 18 months there was swelling of the knees which at another hospital was thought to be due to "kidney trouble" (?). At about the same time the eyes became affected, for which the patient attended Moorfields Eye Hospital for 3 years but without marked benefit. The eyes were rarely inflamed but there was a constant "*running of tears. At the age of 5½ he came to Great Ormond Street, the eyes still giving rise to a certain amount of trouble.* The first blood test was quite negative, but a later one (about 8 months afterwards) gave a partial positive, which however in the light of subsequent investigations came to be regarded as a "false-positive" for 10 later tests during as *many years were consistently negative.* At the age of 7 the eyes became definitely inflamed and our ophthalmic surgeon regarded the patient's condition as "a typical clinical case of I K. with now a central nebula." As, on the strength of the partially positive W R. the patient had been given 12 injections of neo-kharsivan notwithstanding which an attack of typical I K occurred, it was suggested that tuberculin might be tried if and when a further attack of I K came on. The attack duly arrived a month later (Oct. 1923), tuberculin was given but without any obvious benefit The following year the eyes relapsed again when the tubercle complement fixation test was carried out—with an entirely negative result. The patient was seen again at the age of 18 and more recently at the age of 32, when he was perfectly well and reported that his mother and sisters were also in good health His father had been killed in 1917

The probable explanation is that the patient had a mild syphilitic infection derived from the father whose own infection had been mitigated by treatment (p. 297).

The iris and ciliary body

Iritis was formerly not uncommon in syphilitic infants, for Jonathan Hutchinson reported 23 cases (18 in girls, 5 in boys) in his classical memoir (1863) Modern authorities have not encountered the condition so frequently as Hutchinson did and we had very few cases in our series The *exudate in the iris may be so pronounced as to give it a yellow colour and* lead to the diagnosis of pseudoglioma. We have records of two patients in whom the eye had been removed in infancy or early childhood for this *condition In one case* pseudoglioma is stated to have been present at 10 months at 2½ years the eye became inflamed and was removed. The patient (a girl) developed interstitial keratitis in the remaining eye at 9½ years. In the second case pseudoglioma was diagnosed in infancy and the eye removed at 7½ months. Pathologically the eye was said to show metastatic retinitis with vitreous haemorrhages No blood test was taken and the patient received no antisyphilitic treatment When seen by us at the age of 6½ years, she was nearly blind in the remaining eye which exhibited nystagmoid movements On examining the fundus our ophthal

mologist observed small patches of choroido-retinitis and a swelling under the disc the nature of which was uncertain. After more than 3 years treatment with arsenicals and heavy metals the girl remained small and underdeveloped, and was still practically blind in her remaining eye.

The occurrence of iritis in older children is rare. We had not more than 6 cases at the most, all in females, in which iritis was the dominant lesion with a slight admixture of keratitis or cyclitis. Our cases all resembled those with typical interstitial keratitis in several respects. One or more of them arose during treatment for some other syphilitic manifestation, such as Clutton's arthritis, paroxysmal haemoglobinuria, etc. one was associated with pharyngeal ulceration a complained of deafness and in 3 of the 6 patients the teeth had either Hutchinsonian or Moon characteristics or both. Four were W R resistant they all had negative spinal fluids 3 of the patients had both eyes affected, 3 only one eye.

It has already been mentioned that inflammation of the uveal tract usually accompanies interstitial keratitis and that some authorities regard it as the headquarters of the condition. In Spicer's series of cases the ciliary body was involved in 48 per cent, the iris in 28 per cent and the choroid in 29 per cent, these figures, he said, being doubtless an under estimate owing to the dense opacity of the affected corneae in some of the patients Keratic precipitates and posterior synechiae furnished the necessary evidence.

The choroid and retina

The examination of the fundus, particularly that of its peripheral or anterior part, in very young children is often difficult and requires patience and experience occasionally it may be necessary to give a general anaesthetic for the purpose. Choroido-retinitis which is almost pathognomonic of congenital syphilis, may occur even during the first year of life. In its early stage minute spots of pigment surrounded by reddish yellow areas, producing the so-called salt and pepper fundus are seen. In a few of our cases the pigmentation was so scanty that it was impossible to say that the condition observed was not an exaggeration of the normal. Usually this mild type of choroido-retinitis responds well to treatment or it remains quiescent but if untreated it may progress and end in choroidal atrophy and defective vision. It may result in blindness if situated near the macula or the optic disc several of our patients were blind in one eye from this cause. The later stages of choroido-retinitis—the cicatricial stage—show the fundus studded to a greater or less extent with black and white irregular areas. After an acute attack of interstitial keratitis, areas of recent choroido-retinitis may be seen grafted on the scars of an earlier inflammation. Sidler Huguenin (1904) described four types of choroido-retinitis which he regarded as being more or less characteristic, but there were variations in the amount of pigmentation within the types and more

than one type might be present in the same patient, giving rise to transitional forms.

These changes in the choroid and retina may be in part due to and/or be accompanied by syphilitic disease of the ciliary and retinal vessels, resulting in a narrowing of their lumen and cuffing by lymphocytes and plasma cells.

The optic nerve

Igersheimer (1927) states that optic neuritis or papillitis was regarded in Neumann's paediatric clinic as being not uncommon in syphilitic infants, one observer (L. Heine) claiming to have found it in 55 out of 60 infants. Igersheimer's own investigations did not confirm Heine's findings. Optic neuritis may rarely occur in early infancy it usually responds to antisyphilitic treatment, but if untreated it results in optic atrophy. Lesions of the optic nerve are rather more frequently observed in older children than in infants, and may present as a primary optic atrophy—with or without tabetic symptoms—or as an atrophy secondary to papillitis retrobulbar neuritis, basal meningitis or a choroido-retinitis (see p 315) Syphilitic basal meningitis may involve the optic nerve or the visual pathways by the pressure of exudate, by infiltration and later by constriction of the fibrous tissue. As in the case of the brain the lesions due to syphilis of the eye may be many and varied, sometimes very localized at other times scattered or extensive. They may be the result of vascular lesions, pressure of infiltrations or exudates toxins and degenerative changes, secondary to inflammations and vascular episodes Hence may follow papillitis with secondary optic atrophy ophthalmoplegia interna various pupillary anomalies and sometimes visual field defects Visual field defects, which are suggestive early signs of optic atrophy are difficult to assess in young and probably unco-operative children.

Secondary or consecutive optic atrophy

At least 13 of our patients showed optic atrophy of whom 5 have already been referred to under congenital tabes. The optic atrophy was primary in 4 cases and secondary to a severe early choroiditis in the fifth case (see footnote, p 315) The remaining 8 cases were regarded as being secondary to choroido-retinitis or to optic neuritis, 5 of which had negative spinal fluids. On the other hand, five of the spinal fluids from 6 patients with congenital tabes were serologically positive. It would appear therefore —although our numbers are too small to justify any conclusions being drawn from them—that patients with *primary* optic atrophy and with signs or symptoms of tabes dorsalis are more likely to have positive spinal fluids than are patients with *secondary* optic atrophy and little or no apparent involvement of the central nervous system

A brief account of our cases with secondary optic atrophy will be of interest as exemplifying the varied types of congenital syphilis in which secondary optic atrophy may occur

(1 & 2) A sister and brother were examined routinely at the ages of $4^{11}/_{12}$ and $1^{11}/_{12}$ years respectively because a younger brother was found to be suffering from infantile congenital syphilis. The two older sibs had been healthy babies, yet when seen by Mr J H. Doggart widespread choroidal changes, with partial optic atrophy were present. Both children had negative spinal fluids and positive blood W R. s, which reversed to negative after 2 years' treatment with arsenicals and heavy metals. (3) A girl with a squint at 1½ years was found to have optic atrophy consecutive to choroido-retinitis. Her spinal fluid was positive, with a weak W.R. and 10 cells per c.mm. (C.S.F grade 2). (4) A lad of 15¾ years was practically blind in the right eye from atrophy following optic neuritis and choroiditis. He had I.K. at 6 years of age but was not seen by us until he was $8^{4}/_{12}$ years old. He was then deaf and had scarring of his palate and nasopharynx, with perforation of the palate. He was given a considerable amount of treatment (arsenicals and mercury), but his spinal fluid was not examined until he was seen again at 15¾ years. It was then normal except for a slight pleocytosis (10 per c.mm.). The fluid was re-examined at 39¾ years, when it was normal in all respects. (5) The fifth patient, born prematurely as the result of an air raid in the first world war had choroido-retinitis, partial optic atrophy and nystagmus. The S.W R. was strongly positive, the C.S.F normal in all respects. After a considerable amount of treatment with arsenicals, bismuth, malaria and intracisternal injections, the S W.R. became negative, but the patient became mentally defective, so that in the end she had to be sent to an institution for defective children. (6) The sixth patient had a fit at 6 months and when seen by us at the age of $1^{4}/_{12}$ years he was unable to sit up owing to general hypotonicity of the muscles. The pupils were fixed, so that the child was thought to be blind. At Moorfields Eye Hospital secondary optic atrophy in both eyes had been recorded. The S.W R. was strongly positive, the C.S.F normal, despite the fact that the patient was mentally very defective. After 5 courses of sulfarsenol (6·5 G) and mercury the S.W R. became negative, but in view of the apparently hopeless mental and physical condition of the patient—Sir Thomas Fairbank stating that the condition was hopeless so far as surgery or appliances were concerned—further treatment was ruled out. (7) The seventh patient was seen at the clinic at the age of 8½ years, having been brought from an outlying town. There had been no infantile symptoms suggestive of congenital syphilis, but until the child was a year old, the head, arms and legs were constantly on the move." At the local hospital the condition was ascribed to rickets. He did not walk until he was 5 years old. At 8½ years, when he was brought to Great Ormond Street, the first clinical diagnosis was simply mental deficiency " but on closer examination the patient was found to have a large head, with frontal bossing, a depressed bridge to his nose, a convergent squint and poor sight. The eyes were incessantly on the move. The ophthalmologist reported "Choroido-retinitis present and possibly also some optic neuritis but not primary optic atrophy The C.S.F gave a strong W R. and the Lange curve was paretic. The diagnosis was congenital paresis, from which the boy died in the infirmary of his native town at the age of $10^{2}/_{12}$ years. His syphilis had been unrecognized and consequently untreated until he was 8½ years old. (8) The eighth patient was late in crawling and walking, and developed a left hemiplegia at the age of $1^{7}/_{12}$ years. The S.W.R. was not

examined till 5 months later when it was found to be positive and the patient was given some irregular antisyphilitic treatment. At $3^{5}/_{12}$ years he had an operation for contracture, and it was only then discovered that he had extensive choroido-retinitis, with secondary optic atrophy. He had been in three hospitals before he was brought to Great Ormond Street at the age of 7 years, when his condition was as follows. There was a left hemiplegia, knee jerks increased left *more than the right. No syphilitic stigmata.* Teeth normal. Patient was mentally defective, swore and used very bad language. Vision bad. His S.W.R. was strongly positive, the C.S.F. less strongly so, with normal cells and protein and only a slight Lange curve (1123320–0). He was treated energetically with tryparsamide, bismuth, neo-arsphenamine, mercury and stovarsol, with the result that his behaviour improved after treatment was instituted and the blood and spinal fluid eventually reversed to negative, the blood at 12 years and the spinal fluid at 11 years. Nevertheless, *when last seen at the age of 13½* years his vision was still poor and his mental condition showed little improvement. He was then lost sight of owing to the war. This patient's condition which objectively started with a hemiplegia, was undoubtedly the result of a meningovascular lesion rather than a parenchymatous lesion of the brain. This conclusion is based on the finding of a weakly positive C.S.F. in contrast to the more strongly positive fluid with the paretic Lange curve in the seventh patient.

The pupils

Whereas inequality of the pupils may be due to causes other than congenital syphilis, when it is present in a child or adolescent and especially if it should be associated with fixation and or irregularity of one or both pupils, congenital syphilis is the most likely cause. Not infrequently sluggish, unequal pupils may be the only objective sign of congenital neurosyphilis. I have come across cases in children of school age with unequal pupils who were subsequently found to be suffering from latent neurosyphilis, yet who had recently been passed as "normal" by the school doctor. The pupillary anomalies which may be encountered are inequality in size, with or without irregularity, fixed pupils, not reacting to light or to accommodation, and, rarely, true small Argyll Robertson pupils in cases of congenital tabes dorsalis. I have seen patients in whom the relative size of the pupils has varied; at one examination the left pupil has been larger (or smaller) than the right, while on a subsequent occasion, perhaps a month or two later, the reverse condition has been noted. Internal ophthalmoplegia is not uncommon and it is usually bilateral. Occasionally a widely-dilated fixed pupil may be associated with blindness of that eye—amblyopia from want of use, choroido-retinitis affecting the macula, or other cause.

Pupillary anomalies may be an early indication of cerebrospinal syphilis or they may be the result of former activity. The diagnosis between these conditions, which is of considerable prognostic importance, can be determined by examining the spinal fluid at two or three 3-monthly intervals, with intervening courses of treatment.

Strabismus

A squint may occur in a considerable proportion of patients with congenital syphilis, but probably only a few of them are due to the disease itself. We had at least 35 cases of squint in our series, the ratio of convergent to divergent being as 4 to 1. One patient was found to have deficient action of the external rectus muscle of both eyes—probably of central origin—but he had no squint. Of our 29 patients with strabismus whose C.S.F. was examined 18 had a normal, 11 a pathological fluid. Of the latter 9 had a positive W.R., while the other 2 gave a negative W.R. but had increased cell count and protein content. It is noteworthy that whereas the sexes were almost equally affected by squint, 17 males and 18 females, of the 11 with positive spinal fluids no fewer than 10 were females. The incidence of interstitial keratitis and lesions of the fundus were also noted. Ten of the 35 patients had interstitial keratitis, 7 before and 3 after the appearance of the squint, but in this connection it must be stated that few of the patients could be followed up to adult age. Many had already defaulted before the outbreak of the second world war, hence the incidence of keratitis may have been higher than the above figures indicate. Ten of the 35 strabismus patients had fundus changes: choroiditis, choroido-retinitis or pale or atrophic discs; 2 of these patients suffered from interstitial keratitis. One patient, a congenitally-syphilitic mother aged 45 years, suffered from ptosis as well as a divergent strabismus. Several patients also had nystagmus. The presence of a squint in a child, especially if associated with an accommodation or other pupillary anomaly, should serve as a signpost to a thorough investigation of the patient for congenital syphilis. In the series of 35 cases of squint above mentioned 2 were diagnosed by investigating the causation of the squint, which led to the discovery of a tell-tale disseminated choroiditis.

Nystagmus

We had at least 19 patients in our series who showed nystagmus. Nine of them were under 2 years of age, 2 between 2 and 3 years, 7 between the ages of 6 and 11 years, and one a congenital mother whom we saw once only at 19 years of age. The movements were variously described in the case-histories of our patients as "oscillatory", "coarse vertical", "marked nystagmus to the right or left", and "wide nystagmoid movements on attempting to fix". In one case nystagmus was more marked in one eye than in the other, and in another of our cases only the left eye was affected. In 3 patients the fundi were not abnormal and the nystagmus was associated with neurosyphilis, for one case had a relapsing W.R. in the cerebrospinal fluid, a second had slightly increased cells and protein in the spinal fluid, while the third child, the son of a congenitally-syphilitic mother, had a negative blood and spinal fluid but an asymmetrical head and post

mortem (at 9 months) an internal hydrocephalus. In the 2 cases which survived the nystagmus disappeared in one patient in 6 months after 2 courses of sulfarsenol, and in the other patient in 15 months after 5 courses of sulphostab and 1 course of bismuth injections. Several of our cases showed ophthalmoscopic evidence of diffuse choroiditis or choroido-retinitis and in these the examination of the cerebrospinal fluid usually gave negative results. Three exceptions to this general statement patients who had strongly positive cerebrospinal fluids, were (1) a child of 2½ years who was a hopeless ament (2) a girl of $9^2/_{12}$ years with primary optic atrophy and congenital tabes and (3) a boy of 8½ years who died at the age of $10^2/_{12}$ years of congenital G P I

The details of a few of our most interesting cases are as follows

(1) A girl of 8 months had an "oscillatory" nystagmus which was found to be due to a diffuse choroido-retinitis with much vitreous opacity A general anaesthetic was needed to make a satisfactory examination of the fundus. The W R. was strongly positive in the blood and spinal fluid and became negative in the latter in 4 months after 15 injections of bisoxyl. At the age of 18 months the nystagmus had disappeared. The S.W R. became negative in $2^1/_{12}$ years. (2) A girl was seen at 5 months, when the mother complained that the child "rolled her eyes. On examination the patient was found to have a somewhat enlarged head a vertical nystagmus with no fundus changes. The S.W R. was strongly positive, the C S.F negative. After 2 courses of sulfarsenol injections with mercury iodide by mouth the nystagmus disappeared at the age of 11 months. Subsequently however at the age of 20 months, the cerebrospinal fluid became positive (after having been negative and normal in all respects when it was first examined at the age of 5 months). After 20 injections of bismuth metal (10 ml.) the spinal fluid was found to have become normal in all respects at the age of $2^4/_{12}$ years, but the blood was still strongly positive. At the age of 3½ the C S F again relapsed, and the child was treated with T.A.B. vaccine followed by malaria, as the veins were too difficult to continue the intravenous T.A.B injections. After further sulfarsenol injections the blood and spinal fluid became permanently negative at 5 years. The patient was seen repeatedly until she was 12 years old, when she appeared to be a well-developed, healthy girl It is of interest to relate that the patient's mother was herself a congenital syphilitic, her father having died of general paralysis. (3) A third infant had nystagmus at 8 months associated with spasmus nutans. The spinal fluid was not examined at the time but at the age of $4^8/_{12}$ years after a full course of treatment with neo-arsphenamine and mercury iodide the blood and spinal fluid were both serologically negative. At the age of 7 years the right eye showed macular retinitis. (4) A fourth nystagmus case was of considerable interest. A male infant was seen at the age of 15 months, as he was thought to be mentally deficient. There was a history of an abortion at 3 months in 1917 and the patient was born in January 1920. He had snuffles and a rash at 3 weeks, but there was no record of any blood test or of antisyphilitic treatment of himself or his mother On examination he was found to have a big head and the S.W R was strongly positive He was treated with neo-arsphenamine (neo-kharsivan) and mercury iodide and after 4 courses the S W R. became negative at 2½ years and gave 13 negative results until the patient was last seen at $12^3/_{12}$ years. Despite the negative S W R. and a normal spinal fluid at the age of 4 years, the patient's progress was punctuated by several setbacks, for at the age of 2 and

again at 3½ years, he had convulsions, in the last of which he is said to have passed urine and faeces. At 3 years, when the mother reported a "great improvement" in the child's condition, she stated that his eyes seemed to irritate." No serious notice was taken of the eyes till the boy was nearly 5, when it was reported by the mother that he "frowned, and saw better in the dark than in the light. It was then ascertained that there were wide nystagmoid movements on attempting to fix objects, and under an anaesthetic Mr Doyne reported as follows "R.E. Large white swelling in the macular region. L.E. Small white swelling with some pigmentary disturbance. ? glioma. Macular vision must be interfered with." Four months later the macular lesion was noted as being quiescent. Two years later vision was about the same and the patient was attending a myopic school. At the age of 12½ the lad was seen again, when the ophthalmologist found no change in the fundi and the condition was quiescent. Slight lateral nystagmus was still present (1932) He was attending a myopic school till the age of 14, when he was lost sight of.

In support of our observations that nystagmus may improve and even disappear under antisyphilitic treatment, it may be mentioned that Hochsinger Igersheimer and others have recorded similar observations, which appear to show that nystagmus may be luetic in origin. Igersheimer states, however that there is at present (1951) no anatomical proof of this assumption.

Syphilis and blindness

As long ago as 1863 Hutchinson had observed and described the occurrence of blindness in patients suffering from congenital syphilis. He related the case of a young woman of 18 who had been blind in the left eye all her life, which he says may have been the result of an attack of iritis or choroiditis in infancy Five other cases he described, ranging in age from 7 to 24 years, which all showed evidence of optic atrophy

In the early years of this century several Continental authorities, among them Widmark, Igersheimer and Velhagen, found that 8 to 14 per cent of the youthful inmates of institutions for the blind were totally or nearly blind through congenital syphilis (quoted from Igersheimer 1927) Bishop Harman (1921) in an opening paper on the discussion of The Causes and Prevention of Blindness, stated that syphilis was one of the greatest causes of blindness. Sir Arnold Lawson (1922), in the Final Report of the Departmental Committee on The Causes and Prevention of Blindness, stated that syphilis was responsible for not less than 10 to 15 per cent of all blindness then existing in this country and that the true figures were probably higher

The more recent observations of Marshall and Seiler in Scotland (1942) and of Sorsby (1945) show that although congenital syphilis is becoming less serious than it formerly was as a cause of blindness in children and young people, it still caused 4·7 per cent of the blindness found among 2½ millions of persons living in Glasgow and in S W Scotland. More than one-half of the 152 cases of blindness due to congenital syphilis were due

to interstitial keratitis, the remainder being attributed to choroiditis (26) irido-cyclitis (23) optic atrophy (13) and choroido-retinitis (8). The regrettable finding stressed by the authors was that the mean age at onset in the congenital syphilis cases was 14 years, whereas the mean age at which blindness supervened was 24½ years, a period of 10½ years during which treatment might have been given to ward off the blindness. This parallels the author's experience from the records of the Royal School for the Blind in London and Leatherhead, and the absence of treatment is the more deplorable since energetic treatment given betimes would undoubtedly forestall other late manifestations of congenital syphilis such as deafness and neurosyphilis. Sorsby's estimate of the blindness in the British Isles due to congenital syphilis was 5·3 per cent, and he found that there had been a considerable reduction from this cause, though not so great a reduction as there had been from ophthalmia neonatorum, which was from 30 per cent in 1922 to 10 per cent in 1944.

In the U.S.A. the causes and prevention of blindness have received greater attention than they have in this country. The Summer 1950 volume of the *Sight Saving Review* contains several interesting articles which were abstracted in the November 1950 number of the *Journal of Venereal Disease Information*. One article by Edith Kerby stated that during the 13 year period 1936–1948 syphilis had decreased by 50 per cent among the causes of blindness in the records of residential schools and city school systems all over the U.S.A. Another article by Klauder and Meyer made an appeal to all concerned with the welfare of the blind to take more interest in syphilis as a systemic disease in its public health aspects, its treatment and in the early diagnosis of optic nerve involvement. Another paper by Anne Geddes stressed the importance of the following procedures in attempts at reducing the incidence of blindness due to syphilis: (1) increasing emphasis on the newer types of therapy (2) pre-marital blood tests (3) blood tests in early pregnancy and (4) mass serologies.

That particular issue of the *Sight-Saving Review* also stated that under W.H.O. and U.N.I.C.E.F. supported programmes in seven European countries against syphilis and gonorrhoea, and in similar programmes to be carried out in 1950 for several countries in the Eastern Mediterranean, S.E. Asia and the Americas, eye infections from these diseases would be treated in infants and children. Stress would be laid on serological and clinical examination of pregnant mothers.

Between the years 1932 and 1939 we treated at our clinic 13 patients from the Blind School in London: 3 males and 10 females. In addition to these, at least 20 of our other congenital syphilis patients were blind in one or both eyes (8 male, 12 female). Three of these were at the time or later became, congenital fathers and 5 were congenital mothers. The cause of the blindness was variously stated to be diffuse choroiditis or

other lesion affecting the macula, interstitial keratitis optic atrophy meningitis, a fit, and following infantile glaucoma. Optic atrophy has not hitherto appeared to be so frequent a cause of blindness in this country as in the U.S.A. Possibly further observations on this point by British ophthalmologists, together with a wider application of the W R. may show that, whatever may have been the case in the past, optic atrophy is a more frequent cause of blindness in this country than was formerly believed to be the case.

Sometimes the patient is unaware of the fact when he or she is discovered to be blind in one eye one of our cases was discovered accidentally on routine school examination In many instances, particularly those due to disseminated choroiditis and to optic atrophy vision becomes gradually impaired and may eventually be entirely lost. On the other hand, two of our Blind School patients improved to such a degree under antisyphilitic treatment that they could no longer be allowed to remain inmates of the school.

Whatever the incidence of blindness due to syphilis may have been in the past, there is no doubt that of late years the number of syphilis-blinded persons has fallen considerably in this, as in several other countries Nevertheless there are still several thousands of these unfortunate individuals in this country alone and in countries where facilities for the diagnosis, prophylaxis and treatment of congenital syphilis are less readily available, the numbers of syphilitic blind must be tragically and unnecessarily high.

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AFFECTIONS OF THE EARS

The ear is frequently affected by congenital syphilis and since the foetus suffers from a generalized treponemal infection the auditory apparatus may be attacked at quite an early stage of development. As a result syphilitic infants may be deaf from birth and in consequence suffer from *deaf mutism*. *Jonathan Hutchinson* was the first to draw attention to the diseases of the eye and ear which are met with in congenital syphilis and recorded the incidence of 23 patients with deafness amongst his 102 cases of interstitial keratitis. Among his deaf patients were 17 who had otorrhoea and 6 who became deaf without any previous history of ear disease and he observed that sometimes the patient became deaf very rapidly He believed the deafness was due to disease of the auditory nerves or of their distribution in the labyrinth and likened the deafness to blindness from optic atrophy

Mayer and Fraser (1936) wrote on the changes found in the internal ear in cases of congenital syphilis and described miliary gummata in the endosteum of the labyrinth and changes in the spiral ganglion and the organ of Corti Ritchie Rodger has made a special study of aural syphilis

in this country and his papers (1937 1939 and 1945) are based upon 500 cases of syphilis, which included 121 patients with congenital syphilis of these 59 were deaf to a greater or less degree. He points out that there are two main types, the early and the late (the *précoce* and the *tardive* of French authors) and that the early type includes two varieties, (1) meningo-neuritis and meningo-neuro-labyrinthitis associated with syphilitic basal meningitis, and (2) oto-labyrinthitis, the effects of which are confined mainly to the labyrinth and the middle ear The late type is mainly a labyrinthitis and occurs generally about the age of 9 years usually succeeding keratitis.

Whether the deafness of congenital syphilis comes on early or late has a very important bearing upon speech, because if it affects the child before he or she has learnt to speak deaf mutism is almost certain to follow whereas in the later cases when the child has already spoken the power of speech will be maintained

There has been considerable difference of opinion amongst authorities as to the relation of syphilis to deaf mutism, but from the investigations of Beck, Ramadier and Rodger the proportion of syphilis amongst deaf mutes appears to be about 25 per cent. Our own cases furnish very few instances of deaf mutism, doubtless owing to the fact that such children would probably be taken direct to special schools or clinics for this type of infirmity

With regard to the aetiology of severe deafness in children, meningitis and particularly meningococcal meningitis plays an important part, as is shown by several recent surveys (Macleod Yearsley (1934-35) and others mentioned by Gale (1944)) Gale found that the incidence of congenital syphilis as a cause of severe deafness in children varied from 0·05 per cent in American surveys to 4 5 per cent in London surveys These wide variations in the different surveys suggest that the conditions of investigation or the manner in which the investigations were carried out were not really comparable

Macleod Yearsley in an analysis of over 4,000 cases of educational deafness studied during 25 years (1907-1931), found 6·14 per cent due to congenital syphilis, 187 cases in all comprising 66 boys and 121 girls The age of onset of deafness in congenital syphilis varied from 3 to 50 years the maximum being between 6 and 14 years. The degree of deafness among syphilitic children he found to be usually very serious and the condition not to be amenable to antisyphilitic treatment. Yearsley noted that eye complications (interstitial keratitis (177), iritis (19), choroiditis and choroido-retinitis (5) and a few isolated other lesions—optic atrophy (2), polar cataract, posterior staphyloma, cyclitis and iridocyclitis (1 each)) took first place and usually preceded deafness closely He found however as we also did that there was a considerable time lag between the deafness and the eye trouble and in 12 5 per cent of the cases the latter

came on *after* the deafness. His eloquent plea on behalf of deaf children with special reference to the prevention of deafness and to the institution of the *early* education of deaf children in special deaf schools (from the age of 2½ to 3 years instead of 5 years, as is the rule in this country) has not yet been sufficiently heeded by responsible authorities or by the legislature. Miss Edith Whetnall (1952) is of the opinion that a partially-deaf child should start training as soon as the mother suspects or discovers deafness, even at the age of 6 or 9 months. This training she says must be given continuously by the parents at home under the supervision of a trained teacher of the deaf By 3 years the favourable period is over and if training is not started until then, the child will stand little chance of ever acquiring fluent speech.

The pathology of deafness due to congenital syphilis

Observations seem to show that syphilitic basal meningitis may be associated with meningo-neuritis affecting the eighth nerve. At the same time the internal ear may be affected by the specific inflammation. Of rather more frequent occurrence is oto-labyrinthitis, in which the middle ear is attacked Sudden onset without pain or general symptoms is a characteristic feature of this condition and occasionally the first indication may be slight purulent discharge. Rodger states that such a painless onset may occur in tuberculous otitis media and even in the more common types due to pyogenic organisms. Fournier was of the opinion that a large proportion of all cases of bilateral otitis media in very young children were due to syphilis, but other authorities, including Ramadier and Rodger do not share this view

In syphilitic disease of the internal ear the treponema with its predilection for the periosteum and perichondrium, probably attacks in the first instance the muco-periosteum of the inner wall of the middle ear This is succeeded by definite changes on both sides of the thin party plate of bone, giving rise to suppuration in the middle ear and to invasion of the cochlea, with destruction of the delicate nerve endings in the internal ear The degree of involvement of the internal and middle ear in these cases varies so that at times there may be no discharge from the middle ear at all. Unfortunately for the patient, these early cases are frequently overlooked and the diagnosis is made retrospectively that there was a story of illness usually at the age of 12–18 months and by the time the child is seen by the doctor the hearing has been irretrievably lost.

The later form of deafness in congenital syphilis which is due to a specific labyrinthitis and is usually associated with the notched teeth and interstitial keratitis forming the Hutchinsonian triad, is the most important and largest group of affections of the ear associated with congenital syphilis. In Rodger's series it occurred in 44 out of 121 cases of congenital syphilis and was three times as common as were both the early types put together

The age of onset is generally between 8 and 15 years of age, but it may occur as early as 4 years, and in two of his cases it first occurred at 45 and 47 years of age respectively and in a personal communication to the author Rodger stated (1941) that he had records of 5 or 6 patients in whom the inner-ear deafness started in the late forties. The deafness nearly always supervenes 2 or 3 years after the keratitis. Hutchinson found that females were affected twice as frequently as males and Rodger's series confirmed this observation, which others have also done Tinnitus is very common and the noises may precede the deafness and persist long after all hearing is lost. Vertigo is also a common symptom and occurs in all degrees of severity As regards pathology it is the generally accepted view that this is confined to the labyrinth, without any involvement of the middle ear or meninges. Ramadier and Rodger state that in 20 to 30 per cent of these cases patients were unable to hear a shout.

As regards diagnosis Asherson, who examined a considerable number of my deaf patients, found that some of them showed a tympanic membrane of characteristic colour a leaden blue instead of the normal pearly white. He was also of the opinion that the Hennebert syndrome was not very helpful in diagnosis, although Hennebert himself Alexander and others reported favourably upon it. It is the so-called fistula symptom without fistula." During compression or aspiration of the external auditory meatus patients may become giddy and develop nystagmus. The symptom may be apparent to the patient himself or his friends when during the process of washing and drying the face he happens to compress air in the outer ear when drying out the ear with the towel. Rodger in a personal communication to the author said he was not impressed by Hennebert's syndrome. He used it in most of his cases for quite a long period but he was never satisfied that he elicited a definite nystagmus so he discarded the test.

Deafness is more extreme than is usual in a catarrhal or suppurative otitis media and the degree of deafness depends to a very considerable extent upon the stage at which the case comes under observation Bone conduction is not increased relatively to air conduction as it is in otitis media indeed it is as a rule largely lost except for the low frequencies. Tinnitus also serves to distinguish the condition from otitis media, for young patients do not often complain of noises in the ear The vestibular apparatus as well as the cochlea is almost invariably affected and although the child may not have complained of giddiness, either through having forgotten it or through having paid little attention to it, the objective tests nearly always indicate a complete or partial abrogation of vestibular function." (Rodger) Concomitant syphilitic lesions of the nasopharynx or the scars of such lesions may occur in connection with the lesions of the internal ear In Rodger's 44 cases quoted above, 15 showed nasopharyngeal lesions or stigmata whereas 40 had undoubted evidence of

interstitial keratitis. It is advisable that the otoscopic and functional tests for hearing should be carried out by an aural specialist.

Personal observations

Among our 900 cases of congenital syphilis about 100 suffered from deafness and/or otorrhoea. The cases of otorrhoea outnumber those of middle-ear deafness and it is problematical how many of these otorrhoea cases were of syphilitic origin and how many were due to the ordinary causes of this condition. Nasopharyngeal catarrh which is so frequent an accompaniment of early congenital syphilis frequently leads to otorrhoea, and it is probable that an otitis media in a syphilitic child is less likely than in a non-syphilitic one to be amenable to the usual treatment of the condition and it may lead to subsequent deafness. We encountered but one or two cases of the classical type of syphilitic deafness in which the loss of hearing comes on without any antecedent pain or inflammation and rapidly progresses to complete deafness. Indeed, the number of cases of deafness in our series has been considerably lower than the estimates of most previous writers, which may be ascribed in great measure to the better treatment which the young congenital syphilitics have received since the first decade of this century. One can affirm that very few cases of permanent deafness arose in our patients who had received an adequate course of treatment.[1] The usual age of onset in our series was from 8 to 10 years, but a few of the older cases, who would either have had no (or very little) treatment, and that with mercury, started at 30 to 40 years of age. One of our patients, a girl aged 8½ years, previously very bright, developed high grade deafness suddenly after a blow on the head. Amongst the younger children we found that inflating the ears was sometimes followed by improvement which might be permanent, indicating that the deafness was probably not syphilitic but due to middle-ear trouble. On the other hand, in the syphilitic cases inflation of the ear produces no improvement or the improvement, if it does occur, is short lived and the hearing deteriorates. This was found to be the case with several of our patients.

Deafness was not detected in any syphilitic child under the age of 2 years, but one patient seen at the age of 8½ years is said to have been deaf from birth. Among 465 congenitally-syphilitic patients first seen over the age of 2 years there were 45 cases of deafness, 9·6 per cent. In 43 of these, adequate data are available for further analysis (see Table 27).

In Group I deafness was usually due to catarrhal inflammation or wax in the ear (1 case), and not directly associated with syphilis. The series

[1] One must add the reservation that owing to war conditions and other causes it was impossible to follow up many of the patients who defaulted at from 17 or 18 years of age upward.

TABLE 27

Deafness in 43 Patients with Congenital Syphilis with the C.S.F. Investigation in 31 Cases and the Relation to Interstitial Keratitis in 29

Type of deafness	*Number of cases*			*I.K.*		*C.S.F.*		
	Male	*Female*	*Total*	*Before*	*After*	*Normal*	*Pos.*	*Not exam.*
I. Temporary deafness ("catarrh or wax)	5	6	11	2	1	10	0	1
II. Mixed syphilitic and catarrhal"	4	10	14	9	4	8	1	5
III. Characteristic syphilitic deafness	6	12	18	9	4	12	0	6
Totals	15	28	43	20	9	30	1	12

are about equally represented and keratitis uncommon. In Groups II and III females preponderated and there was a high incidence of interstitial keratitis. C.S.F. changes were seen in only one patient (the mongol mentioned on p. 323) so that the association between neurosyphilis and the blindness due to optic atrophy appears not to be paralleled by a like association between deafness and neurosyphilis. Of the patients in Group II 7 or one half showed marked improvement after antisyphilitic treatment, whereas of those in Group III only a few showed transient improvement and when last seen they were all very deaf. Only a few of our patients in this group complained of tinnitus or vertigo which is apparently at variance with the experience of previous observers.

The following histories exemplify the temporary and permanent types of deafness seen in congenitally syphilitic patients.

Roma A. developed interstitial keratitis (B.E.) at the age of $9\frac{4}{12}$ years, for which she was treated at an eye hospital with mercury. Seven months later she became deaf and when seen at our clinic at 10½ years of age the right eye showed corneal scarring and the left eye was still very opaque. The patient was very deaf, rather pale, and the teeth showed only slight Hutchinson and Moon features. The C.S.F. was normal. Arsphenamine treatment was started and there was definite improvement in the hearing after the first course of injections. After a year's attendance at the clinic, during which she received 4 courses of arsenicals and mercury iodide, the eyes were nearly clear and the hearing had improved still further. In all the patient was given 46 injections (0.6 G. neo-silver-salvarsan and 14·9 G. sulfarsenol) and HgI over a period of 16 months. Three and a half years after the onset of the keratitis the eyes were practically well and the hearing appeared normal (no special tests were made). The W.R. which was strongly positive when the patient was first seen by us at 10½ years of age became negative 4 years later. At the age of 14½ years vision and hearing were normal, but the patient was still anaemic. Two and a half years later I was

informed that she had a relapse of the keratitis at the age of $16^{8}/_{12}$ years, when she was found at an eye hospital to have a relapse of the W R. She was sent to a nearby general hospital for further treatment but did not attend there and her further history is unknown

Mrs. S born about 1880, *brought her son to Great Ormond Street* at the age of $9^{10}/_{12}$ years with the history of right hemiplegia following a fit at the age of 6 weeks. There had been no rash or snuffles and the boy was microcephalic. The mother herself was very deaf but congenital syphilis was not suspected at the time of her first visit to hospital, for one was not on the look-out for parental congenital syphilis in those far-off days (1919). Her W R. was only weakly positive the Kahn test was not done at that time. *Eight years later another* mother and child from the same little town in Kent came to the hospital, and upon inquiry it was ascertained that the mothers were sisters. Whereas the first mother had apparently had no infantile or later symptoms until deafness occurred (at ? age) when first seen by us at about the age of 39 or 40 she was very deaf Nine years later she had severe parotitis which tended to recur during the ensuing 2 and 3 years. Her deafness persisted The other mother who was 5 *years younger than her sister had interstitial keratitis* when she was about 18 and at the same time had arthritis of the knees, probably Clutton s joints. When she first came to us at the age of 45 she had the typical facies of congenital syphilis (Fig 24) and was rather deaf Five years later her deafness had increased but 3 years afterwards, when she was last seen in 1936, her hearing had somewhat improved. Whether her hearing continued to improve or deteriorated she certainly was not an example of the classical syphilitic deafness which comes on suddenly and with tragic progress leads rapidly to complete deafness, as in the girl of 8½ referred to previously

Finally there are several important points in relation to aural syphilis which one would emphasize (1) The best insurance of all, inasmuch as it *would practically eliminate congenital syphilis, is the detection of syphilitic* mothers and their antisyphilitic treatment as early as possible in their pregnancy (2) The next best insurance against syphilitic deafness as of other late manifestations of the disease, is the efficient treatment of the patient as early as possible. (3) Deaf and deaf mute patients in institutions should receive prompt and efficient treatment if they are discovered to be syphilitic. This is rarely if ever undertaken from the prevalent and erroneous belief that such treatment is valueless. While this may possibly be true in many cases as regards the deafness it is certainly unjustified from the point of view of the patient s future welfare. In default of appropriate antisyphilitic treatment, blindness from optic atrophy interstitial keratitis, choroido-retinitis and so forth may ensue and the patient become a blind deaf mute—a truly pitiable plight to be prevented at all costs. (4) A number of young syphilitics suffer from meningitis, usually at from 9 months to 2 years of age and frequently the illness has been simply called meningitis without any thought by the attendant practitioner that the condition might be syphilitic in origin. In consequence no antisyphilitic treatment was given and subsequently the patient had become irremediably deaf or blind or both We saw at least a dozen

such cases in our series and we concluded from our experience that all cases of meningitis and encephalitis should have a cerebrospinal fluid investigation, which should include a serological test.

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THE ENDOCRINE GLANDS

During the past 30 years it has become increasingly recognized that the endocrine glands play an important part in physical and mental development. In the syphilitic foetus and neonate treponemata have been found in all the endocrine glands (McIntosh 1909 Hoffmann 1908 and many others) not only in the interstitial connective tissue but also between and even within the secretory cells. It is not surprising to find, therefore that the development and function of these glands may be interfered with in congenital syphilitics. The functions of the various endocrine glands are closely interrelated, so that it may be difficult to determine which is the most severely affected and in some patients the clinical features may suggest a primarily hypothalamic disorder

In opening a discussion on the Diagnosis and Treatment of Congenital Syphilis," Sir Humphry Rolleston (1921) laid particular stress upon the probable importance of the endocrine glands in the malnutrition and infantilism of congenital lues He pointed out that when one of the ductless glands was damaged the others tended to undergo change also that changes in the endocrine glands might lead indirectly to syndromes which were not necessarily syphilitic in origin

The sex glands

Both ovary and testis in the syphilitic foetus and neonate may contain a considerable number of parasites. In an early paper upon *T pallidum* McIntosh (1909) depicted the parasite in the ova as well as in the interstitial tissue of the ovary In the testis the treponema is to be found not only between the cells and in the lumen of the tubules, but also between the inflammatory cells which result from its presence. Hochsinger has remarked that syphilis of the testicle is much more frequently found upon the histological investigation of syphilitic foetuses and neonates than it can be diagnosed clinically in young infants It was formerly thought that the testis was not affected in congenital syphilis, but several observers towards the end of the nineteenth century (Henoch 1889 Carpenter 1892 Seringe 1899 and others) stated that the organ was affected in a considerable proportion of cases. Carpenter informs us that Seringe from a study of 164 cases, came to the conclusion that syphilitic orchitis might arrest the descent of the testicle and be concerned in infantilism. He found, too that hydrocele occurred in 25 per cent of syphilitic testes, confirming Carpenter's earlier observations upon the subject. Anent syphilitic orchitis, Carpenter stated (1901) that the usual anatomical sources gave practically no information about the healthy testes of infants, and without such information it was impossible to make a diagnosis in some cases. From his own observations he found that the testes vary greatly in size in some children they may be no larger than lemon pips, whilst in others they are the size of hazel nuts. Little growth takes place in them until the age of puberty Between these extremes the variations are numerous. In 1892 he recorded 18 cases of syphilitic orchitis by 1907 he had met with 75 cases of departure from the normal in varying degree. Still observed orchitis in 5 of his 64 male syphilitics (7·9 per cent) in 3 of them at the age of 12 weeks, in 1 at 4½ months and in 1 at 12 months In none of Still's cases was hydrocele a complication of the orchitis.

It is possible that the condition had been becoming less common than it was formerly for it is not often referred to by modern authors as a noteworthy manifestation of congenital lues. On the other hand it may be overlooked owing to the normal variations in size of the testicle stressed by Carpenter particularly if unaccompanied by hydrocele. Syphilitic orchitis may also affect the epididymis, and it is *generally held that an* enlarged testis in an infant below the age of 4 or 5 months is strongly suggestive of congenital syphilis Very rarely there may be a gumma in the testis Dennie and Pakula record a case in which one was present at birth. We did not encounter an *infantile gumma of the testis*, and saw only one case of gumma of the scrotum and testicle—in a boy aged 10—in our series of 436 male cases of congenital syphilis.

Our experience of infantile syphilitic orchitis was that the condition

was not nearly so common as Carpenter had observed it to be for we have records of but 4 cases of orchitis and 6 of hydrocele, 2 of the latter being diagnosed as ? orchitis by the surgeon who saw them. Our 10 cases occurred among 220 syphilitic boys under 1 year (4 5 per cent) Of the 10 cases, 5 were bilateral, 1 affected only the right testis and in the remaining 4 there is no record as to whether one or both organs were affected.

One of our cases of orchitis which came to autopsy showed considerable overgrowth of fibrous tissue (see Fig 90), as is often the case with the



Fig 90 Syphilitic orchitis in a child aged 3 months The spermatic tubules are compressed and reduced in number by overgrowth of the interstitial tissue which is infiltrated by plasma cells and lymphocytes (112)

secretory organs. In the event of the patient's survival such fibrosis would probably result in atrophy of the secreting cells.

Menninger (1928) states that orchitis in congenital syphilis is clinically seen most frequently during the first year of life. It is usually bilateral he says, yet not infrequently unilateral.

In the discussion on congenital syphilis above referred to Sir Frederick Mott stated that in cases of juvenile general paralysis, in which mental, physical and sexual development were usually very retarded, the testes frequently had the histological appearances of the organs at birth, except that the interstitial cells of Leydig were absent. Mott assumed that their absence was related to the absence of the secondary sexual characters.

and to the infantilism He also suggested that treponemal toxins might *depress the vital energy of the testes in cases of congenital syphilis.* We noted that in several of our cases puberty was delayed, the genitalia being infantile in character until 13 or 14 years of age, and it was not until 16 or 17 years that normal development and growth of pubic hair took place. The testis (or ovary) is not the only organ concerned in infantilism in congenital syphilis. Infantilism is almost certainly a pluriglandular condition, the pituitary and possibly the thymus and other endocrine glands, as well as the hypothalamus, being concerned in its causation. Many observers have described cases of infantilism among juvenile paretics and noted that the infantilism was general as well as being genital.

It is recommended that the testes should be carefully palpated in all cases of congenital syphilis in boys, since if they are obviously enlarged, prompt antisyphilitic treatment may lead to resolution of the orchitis, with probable benefit to the patient's physical development and subsequent fertility

In the case of the ovary few if any recorded observations have been made upon structural changes due to *T pallidum* It may be presumed that the effects of the treponema upon the ovary are similar to those seen in the testis, and that growth and development may be retarded In some of our cases menstruation was delayed in its onset and irregular once it had started. These symptoms were frequently associated with under development of the external and internal sex organs. Congenitally syphilitic girls may remain underdeveloped mentally physically and sexually but admittedly it is impossible to say that the condition is due solely to the lack of ovarian hormones. The hypothalamus, the pituitary and other endocrine glands no doubt play a part in this type of infantilism

The ovary is not always severely affected in congenital syphilis, for many congenital mothers are able to bear and rear children. On several occasions, as opportunity offered, we examined the ovary (or testis) for the presence of the treponema, but we rarely succeeded in recognizing it in stained preparations. This indeed is not surprising and is no evidence that the parasite may not have been present in the organ previously for the patients had usually received treponemicidal treatment before death This doubtless led to the disintegration of the parasites or possibly to their *conversion into a non-spirochaetal form.*

The thyroid and parathyroids

The thyroid does not appear to be so often affected as some of the other glands, but the changes produced by the treponema are fundamentally similar Hutinel states that the cells lining the acini may undergo necrosis and be shed into the lumen of the acini together with red and white blood corpuscles. *Later fibrosis takes place, with the result that the gland*

becomes paler in appearance and firmer in consistency Perrando quoted by Laird (1945) described changes in foetal syphilitic thyroids, which he regarded as being diagnostic small round-celled infiltration endarteritis obliterans, diminished colloid, arrested development and glandular enlargement owing to increased interstitial connective tissue. In later stages fibrosis and induration of the gland occur Menninger (1929) writing upon the thyroid in congenital syphilis, reviewed the literature and added 4 cases of his own. In 3 of these, 2 infants and 1 a mentally retarded boy of 9, there was no clinical evidence of thyroid dysfunction, but at autopsy interstitial fibrosis was found in the thyroid as well as in other endocrine glands. His fourth case was a mentally retarded girl of 17 with congenital syphilis (Hutchinsonian teeth and interstitial keratitis) and clinical hypothyroidism. Her W R. was negative, but she improved on arsphenamine treatment.

Gummata of the thyroid have been recorded but they are distinctly rare. Laird (1945) described a case in a congenital syphilitic patient of 42, *who had noticed a painless swelling of the neck for 12 months. In* addition, the patient complained of increasing difficulty in swallowing solid food and of undue breathlessness on exertion The tentative diagnosis was a branchial cyst and a routine W R. gave a positive result. Under cautious administration of sodium iodide and bismuth oxychloride, together with small doses of mapharside, an excellent therapeutic response was obtained. The patient's general physical and mental improvement was marked and the eyebrows, which had been thinning in the outer parts reverted to normal. A somewhat similar case of our own has been referred to on p 139. A girl, aged 10½ years attended Mr George Waugh's clinic on account of a swelling in the front of her neck. The surgical diagnosis was either a gumma or a branchial cyst, but apart from its position there were no signs or symptoms to suggest that there was any disease of the thyroid. A therapeutic test showed it to be a gumma.

We encountered only one patient with exophthalmic goitre in our series of congenital syphilitics His history was as follows

Leslie W., born in 1924, an only child, the mother having had no previous miscarriages. There was no history of infection in the parents before the birth of the patient, but the mother had a "bad throat and a nervous breakdown when the infant was 3 months old. He had no infantile symptoms of congenital syphilis, but at 4 years he had "suppressed measles," enlarged tonsils and cervical adenitis. At 7½ years he suffered from I K. (both eyes) for which he was treated with stabilarsan and mercury at an eye hospital. At the age of 8¹⁰/₁₂ years he attended Dr Paterson's O.P Clinic at the Children's Hospital when his teeth were found to be typically Hutchinsonian and Moon, the W R. moderately strong (4.3.0.0.) and the C.S.F normal in all respects. Shortly afterwards, at 9 years of age, the thyroid showed considerable enlargement, the eyes were rather staring hands tremulous, but there was no increase in the pulse rate. The isthmus of the thyroid was easily palpable He was given 16 G neo-arsphenamine with mercury iodide by mouth and 30 ml. bismoxyl between the ages of 9½

and 10½ symptomatic treatment with bromide was given for the thyroid. By the age of 11½ there remained little evidence of thyroid over activity and the gland was becoming smaller At 12 years the W R. was negative following a further course of bisoxyl (30 ml.), and when last seen at the age of 14½ he was a well-developed, normal lad.

Although in this patient mild transient thyrotoxicosis complicated congenital syphilis, it cannot be claimed that the thyroid condition was due to syphilis. Of our 465 patients with congenital syphilis over the age of 2 years, this was the only case of its kind and the association of the two diseases must be considered to have been fortuitous.

Hypothyroidism

It is asserted that congenital syphilis patients often suffer from hypothyroidism (Hutinel and other French writers Gordon and others) and acting upon this assumption we supplemented the antispecific treatment of some of our patients with thyroid medication, but our data do not permit us to assess the value, if any of the additional thyroid therapy Facilities were not available at that time for ascertaining the basal metabolic rate which would have enabled us to carry out our observations more scientifically

The **parathyroids** may be affected by congenital syphilis, together with the thyroid collections of lymphocytes and plasma cells and increase of connective tissue may be seen, with occasional haemorrhages. Hutinel and other French authors maintain that syphilis of the parathyroid glands may give rise to tetany As these glands are intimately concerned with *the regulation of the amount of blood calcium and its distribution to the* tissue, it has been suggested by A. T Pitts and others that the parathyroids may have an effect upon the development and calcification of the teeth

The **thymus**, in addition to having a lymphoid structure, is possibly an endocrine gland which functions during the early years of life Little is known about its action but it appears to exert a markedly stimulating effect upon the growth of young animals. Dubois, in 1850 described minute abscesses in sections of the gland and Henoch has stated that he found such abscesses on two occasions. These may have been fortuitous, for during the past 50 years there has been no record of such abscesses having been present, and it should be pointed out that abscess formation is not uncommon in congenital syphilitic infants, and this might quite as well occur in the thymus as in any other part of the body

The adrenals

The predilection of the treponema for the adrenals is stated to be second only to that for the liver and in sections the parasites may be found in enormous numbers. In Mewis's material referred to on p. 173 the

adrenals were found enlarged and diseased in 19 per cent of the cases. Histological changes in these glands were first reported by Von Bärensprung (1864) and his findings were confirmed by Parrot, Henoch and others. Macroscopically the glands are enlarged, grey or whitish in colour with miliary syphilomata on the surface or in the substance later they may become fibrotic. Microscopically the usual syphilitic lesions were seen changes in the vessel walls, increase in the perivascular connective tissue, round-cell infiltration in the lacunar spaces, changes in the cells and increase of interstitial connective tissue. Function is usually affected and, according to Hutinel, the cortex is more affected than the medulla. Clinically lowering of the blood pressure and asthenic symptoms ("Addisonism," of French authors) may result from involvement of the adrenals, and Hutinel is of the opinion that when congenital syphilitic patients suddenly take a turn for the worse, hypofunction of the adrenals may be the cause. This is only his impression and he adduces no evidence in support of his opinion. Our own histological and pathological observations furnish insufficient data for a definite opinion on this point, but to judge from the potent action of cortisone and other derivatives of the adrenal cortex and medulla, it may well be that interference with the function of the adrenals might turn the scales against a syphilitic infant.

The pituitary

The pituitary may undoubtedly be affected in congenital syphilis in two ways (1) directly as may any gland by the action of the treponema, and/or its presumed toxin, upon its cells, blood vessels and fine intercellular tissue and (2) indirectly as a result of basal meningitis, which is sometimes met with in cases of early congenital syphilis. The structural changes, cellular and vascular are similar to those described in connection with other glands, including areas of necrosis miliary syphilomata and increase of interstitial tissue. Schmitt (1923), in an examination of the pituitary gland in 34 foetuses and neonates with proven or suspected congenital syphilis, found that 16 showed histological appearances in the anterior lobe which were suggestive of the disease. These he summarized as varying degrees of interstitial inflammation with more or less extensive necrosis in three of the cases, one of which showed marked calcification. Three other cases exhibited small areas of calcification but without necrosis. These changes if severe might lead to pituitary dysfunction, but the activities of the pituitary hypothalamic axis are so complex that it is difficult in many cases to relate symptoms to disturbances of individual hormones or functions. The cases of this series were seen between the years 1917 and 1938 and the views expressed at that time on endocrine problems make curious reading to-day—so rapid has been the progress in this branch of medicine. However certain groups of cases were seen which fell into well recognized types and these will be described.

I *Diabetes insipidus* We have seen no case of frank diabetes insipidus, but encountered 3 cases of severe but transient polyuria possibly of similar origin.

The first patient was a boy aged 12 who developed this symptom after a fall during which he injured his head. His case has already been referred to on p 169 since he suffered for a time from hepatic cirrhosis. His polyuria was transient and was no doubt due to a temporary functional disturbance of traumatic origin. There had probably been no basal meningitis in this case, as the C S F had been found quite normal at 8¼ years and again when he was warded because of the polyuria.

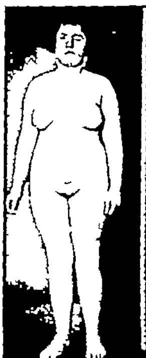


FIG 91 Gross obesity in a syphilitic patient at 11 years of age She had neurosyphilis and her mother died of general paralysis at 44 years (The after history of the patient and her father were unascertainable owing to the war)

The second patient developed transient polyuria at the age of $12^{5}/_{1}$ years. The lad subsequently developed juvenile general paralysis, from which he made a good recovery (see p 306) As there was manifest neurosyphilis in this patient it is possible that basal meningitis may have temporarily affected the hypothalamic pituitary connections.

The third patient who suffered from polyuria began to do so at the age of $2^{1}/_{12}$ years His case was interesting from many points of view He was an illegitimate child who was brought to hospital by his grandmother who later developed a gumma of the scalp when her W R. was found to be strongly positive The boy may therefore have been a case of third generation syphilis, but we were unable to induce his mother to attend the clinic, when we could have examined her to see if she showed any signs of the congenital disease At the age of 14 months his little fingers were noticed to be curved and his attendant physician thought his face was of mongolian type. His deciduous teeth were definitely notched (see p 147) At the age of $2^{1}/_{12}$ years, when his polyuria started, the hands were noticed to be enlarging and a pituitary lesion was thought to be the most likely cause The C S F was normal in all respects and 6 weeks later the patient was passing less urine though enuresis persisted for several years. He was backward at school though it was difficult to assess how much of this was due to his mental condition and how much to the social conditions under which he was

being brought up by his grandparents, as they were living in a remote village in the country

II *Obesity* We had 6 cases of gross obesity which were diagnosed by their physicians as being due to dyspituitarism Details are given in Table 28 It will be noted that all the patients were girls obesity developed between the ages of 8 and 15 years. Five of the 6 patients had an abnormal C.S.F with a positive W.R., but the fact that all the patients menstruated—one at the age of 9 years and the others between 13 and 14—is against a pituitary hypothalamic basis for the obesity It is noteworthy that 4 of the patients were mentally defective and another was blind

TABLE 28

Congenital Syphilitic Patients with Gross Obesity

Age when first seen	*Year*	*Clinical manifestations or diagnosis*	*Blood W.R.*	*C.S.F W.R.*	*Remarks*
1. S.S. ♀ [illegible]/12	1923	Short and fat, which suggested hypopituitarism.	+ + + + at [illegible]/12 Still pos at 22, neg at 24 yrs.	+ + + +, all else normal at 9 [illegible]/12 W.R. neg. at 22 yrs.	Anaemic at 22 (1937). Otherwise [illegible] at 25 yrs.
2. L.P. ♀ 1 [illegible]/12	1926	Obesity spade-like hands, epileptiform attacks. Diagnosis hypopituitarism, ? thyroid deficiency by Dr Cockayne, G.P.I. by Dr Wythe.	+ + + + at 1 [illegible]/12 Neg at 5 and 20 yrs.	+ + + + at ½ Lange curv paretic. W.R. neg 15 and 20 yrs.	Treated with malaria and intraventricular injns. Salvarsanised serum. Bld. and C.S.F normal but fits continued and pt. died— cured G.P.I at 22½ yrs
3. E.G. ♀ 9½	1931	Always mentally retarded Now emotional, spastic, tremulous, G.P.I	+ + + + at 9½ Neg at 3 yrs.	+ + + + at 9½ Lange curve tabetic Neg at [illegible]/12 yrs.	'G.P.I cured' Fits continued Pt. died 5½ yrs Mother also died G.P.I aged 38 yrs
4. L.W. ♀ 6 10/12	193[illegible]	Syphilitic pachymeningitis and myelitis diagnosed Legs spastic Mentally retarded. Getting fat at 2.	+ + + + at 6 [illegible]/12 Neg at 7 10/12 yrs	+ + + + at 10/12 Lange curv paretic Neg. at 4½ yrs	Seen at ½ looks about 6 [illegible] simple and cannot concentrate
5. D.E. ♀ 9 4/12	193[illegible]	Hutchinson triad. Became very fat at 5½ (? dyspituitarism).	3.o. K.P.P at 9 4/12 Neg. at 4 yrs.	Neg at 10 3/12 yrs	A Blind School patient Early history indefinite.
6. M.W. ♀ 7 10/12	1933	Fat from 6 yrs. onwards. Gradually became very fat and at 3 was colossal (see Fig 9 and p 303).	+ + + + at 7 10/12 Neg at to 6 4/12 yrs.	+ + + + at 8 Lange curv paretic T + + at 8 [illegible]/12 yrs. Not examined later	Pt. started menstruating at 9 yrs. Dr Raymond Greene advised against endocrine therapy at 6 4/12 yrs. Mother died G.P.I. at 44 yrs

III *Infantilism* Infantilism may be seen in children with any chronic debilitating condition, without direct involvement of the pituitary gland

It is not unlikely that congenital syphilis may similarly interfere with normal development. However the finding of histological evidence of pituitary lesions in syphilitic foetuses and neonates suggests that in some cases there may be a more direct causation. Infantilism associated with dysfunction of the gonads has already been referred to. We had only one case of true infantilism in our series, and this was in all probability of pituitary origin.

N. O. was born in 1918 snuffled but had no rash or epiphysitis in infancy. She developed normally until the age of 6 months, after which growth was retarded. The mother stated that her doctor gave the child 3 intramuscular injections which are said to have reversed the blood reaction. At 2 years she was very small for her age, passed very pale motions and was thought to be suffering from coeliac disease. When we first saw her she was 4 years old and her W. R. was strongly positive. After 2 courses of sulfarsenol (2·5 G.) her W. R. quickly became negative and it was repeatedly negative until last tested at the age of 19 years. Her C.S.F. was normal when tested at 6²/₁₂ years. X-ray examination of the epiphyses at 7 years showed nothing abnormal and an X-ray of the skull at 15 years of age showed that the pituitary fossa was normal and the dentition was normal except for the absence of the lower premolars and the lower left first molar (Dr. Shires).

Between the ages of 7 and 13 years the child was examined by Sir Frederick Still, Dr. Cockayne and Dr. Frew, the only one to venture a constructive suggestion being Dr. Cockayne, who thought she might be suffering from hypopituitarism possibly affecting the anterior lobe. She was given various glandular products by mouth, Armour's thyroid, hormotone and dried pituitary, but with disappointing results. Table 29 shows the stages in her development. The

TABLE 29

The Height and Weight of a Congenital-Syphilitic Pituitary Dwarf at Different Stages of her Development

Date	*Age*	*Height*	*Weight*
XI 1925	7/12 years		26½ lb. (12·05 kg.)
VIII 1929	4 years	40 in. (1·016 m.)	33½ lb. (14·6 kg.)
VII 1930	2¹¹/₁₂ years		40 lb. (18·18 kg.)
XII 1932	4 11/12 years	42¼ in. (1·073 m.)	42¾ lb. (19·43 kg.)
XII 1933	15/12 years	43 in. (1·092 m.)	46¾ lb. (21·25 kg.)
IX 1935	7⁴/₁₂ years	46 in. (1·168 m.)	51¾ lb. (23·52 kg.)
IV 1936	17¹/₁₂ years	46½ in. (1·181 m.)	52½ lb. (23·86 kg.)
IX 1937	8 1/12 years	47 in. (1·193 m.)	55¼ lb. (25·11 kg.)
III 1945	26/12 years	48 in. (1·219 m.)	

patient was mentally bright and in fact acted in an annual pantomime for some years, taking a child's part although she was then 15 to 18 years old. When she was nearing 27 years of age she wished to get married, not with a view to having children but to satisfy a desire for sexual intercourse. The man of her choice was 5 ft. 8 in. (1·727 m.) while she herself was only 4 ft. (1·219 m.). I felt personally unable to advise the patient in the matter and Professor F. J. Browne, the gynaecologist, kindly consented to examine her and advise accordingly. His opinion was that the anterior pituitary lobe had undergone fibrous

and that the patient had primary and probably permanent, amenorrhoea. Her genital organs were those of a child and with a vagina of its then size con nection would be impossible for an adult man. The only suggestion he could make by way of treatment was to give her a course of synapoidin, which is a synergistic compound of pituitary substance with gonadotrophic hormone and might start her ovaries working [1]

In addition to this case of infantilism there were two unusual cases of delayed development in boys.

The first boy attended the Children's Hospital for snuffles in 1916 when he was under the care of Dr Robert Hutchison. He attended for a year and was doubtless at the time given mercury treatment. At the age of 7 years he attended Dr Cockayne's clinic and was diagnosed "infantilism." The mother's obstetric history was rather suggestive of syphilis, so she and the child were examined serologically The mother's blood was W.R. negative the boy's weakly positive, on the strength of which he was given a course of neo-arsphenamine. Three subsequent Wassermann tests of the boy's blood were negative and in view of the mother's negative W R. it was thought that syphilis was probably not the cause of the infantilism. He remained small and was somewhat anaemic at 17 he had the size of a boy of 9 or 10 and the Labour Exchange considered him "almost unemployable, being so small and unintelligent.' In 1937 at the age of 22, he was still small and "had no strength or mental ability" In 1943 his mother wrote to the hospital to thank them for all that had been done for the lad (!) she added he was "now aged 28 and a fine fellow in the Royal Air Force. When he first came to the hospital he weighed hardly 2½ pounds." There are no available records of the condition of the sex organs at the various epochs of his life or of their ultimate development, and whatever the cause of the early state of infantilism may have been, Nature seems to have played a dominant part in the treatment of the patient's condition.

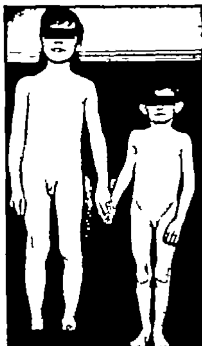


FIG 92. A case of infantilism in a boy aged 9 years photographed with a normal boy of the same age The small boy had a syphilitic mother and step-sister and his mother had not received any treatment before he was born He had a negative W.R from [illegible]/12 to 15[illegible] 12 years

[1] The second world war being then still on, the patient would not come into hospital for the treatment suggested. Professor Browne in a subsequent communication (1952) wrote that synapoidin in similar cases gave disappointing results, so he imagined that the drug would have little or no effect.

The second boy was half brother to one of our congenital syphilis patients his mother's blood was W R. positive and she had been given no treatment before the birth of either of the children. He was small at birth (wt. 4 lb., or 1 87 kg) and at one year he weighed only 10½ lb (4·7 kg). He showed no symptoms of congenital syphilis and his slow growth was thought to be possibly due to syphilis in the mother He was given antisyphilitic treatment and various hormones by mouth, but with no dramatic results. At $8^{10}/_{12}$ years he weighed 32 lb (14 5 kg), and his diminutive size beside a normal boy of his age is seen in Fig 92. When last seen at the age of 16½ years his weight was 70 lb (31 5 kg) and his height just under 5 ft. (1 524 m.). Pubic hair was present, but the testes were small, though not infantile. There is no evidence of hormonal dysfunction in this case and the slow development of the boy may have been the result of a "syphilitic soil" or on the other hand, it may have been fortuitous.

In addition we encountered nearly 50 cases in which the children were small and showed some degree of infantilism. Details of these patients are given in Table 30 Of those who were noted to be small in childhood

TABLE 30

Forty-seven Small Congenitally-Syphilitic Patients in Relation to Positive Spinal Fluids

Type or category	*Cerebrospinal fluid*			*Total*	*Remarks*
	Neg	*Pos.*	*Not examd.*		
1 Small at birth	3	1	1	5	
2. Small in infancy	7	2a	0	9	a. One was latent neurosyphilitic. The other was a grade C.S.F with wt. only 23 lb. (10·4 kg) at 3 yrs.
3 Small in childhood or later	15	11	7	33	
	25	14	8	47	

or later at least one-third had positive spinal fluids. It is, however more likely that this is an indication of the seriousness of their illness than that it points to a hypothalamic or pituitary basis for their condition, and the fact that 2 of them were congenital mothers is against any severe disturbance of pituitary function. It is of interest to note that 4 of these patients had parents with G P I or tabes and that 3 were children of congenitally syphilitic mothers.

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CHAPTER 9

THIRD-GENERATION SYPHILIS

For many years syphilologists have discussed the question of third-generation syphilis from at least two points of view. Firstly as to whether it occurs at all, and secondly if it does occur whether it does so with sufficient frequency to be of any practical importance. With regard to the first problem the majority of observers are of the opinion that third generation syphilis can and does occur although by a few its occurrence has been emphatically denied. A. Fournier in 1891 wrote "Acquired syphilis may be transmitted to the offspring 18 to 20 years after the infection, and there is no valid reason why hereditary syphilis might not be transmitted by a woman of 18 to 20 years of age." He concluded by saying that while the transmission of syphilis to the third generation is *logically possible, its occurrence had not yet been indisputably demonstrated.* He made the conditions of proof very stringent: evidence of syphilis in the grandparent, evidence of early inherited syphilis in the parent and child (that is, the second and third generations), and also evidence that syphilis had not been acquired by either of the parents (second generation). Subsequent French authors regarded third-generation syphilis as a not infrequent occurrence, but the evidence adduced in support of their thesis was often unconvincing, a number of congenital malformations such as cleft palate, harelip and hernia, as well as various dystrophies, being regarded as evidence of a syphilitic nature even though the S.W.R. was negative. Finger (1900) came to the conclusion that third-generation syphilis must be regarded as being theoretically possible, but that there had been no indisputable evidence of its occurrence. The conditions which he held to be essential for its demonstration were even more stringent than those of Fournier.

While these conditions might be considered necessary to demonstrate scientifically the presence of third-generation syphilis, the majority of observers would agree that it seems unnecessary, *for example, to require* the symptoms of syphilis in the second generation to occur soon after birth. As Igersheimer and others have pointed out, the presence of interstitial keratitis or the presence of the well known stigmata of congenital syphilis, such as typical Hutchinsonian teeth, are in themselves, if not absolutely diagnostic of congenital syphilis in the individual, at least

highly presumptive of it. It is a well known fact that the fathers of congenitally-syphilitic children, who presumably have introduced the infection into the family in many cases either give no history of infection or may have a negative W R. so that it is difficult to satisfy the postulate that syphilis in the second generation must be absolutely excluded.

The opinion of English authorities at the turn of the century was largely influenced by that of Jonathan Hutchinson who in the last edition of his work Syphilis (1909) says that he is absolutely incredulous as to the inheritance in the third generation." It should be pointed out, however that later on in the same chapter he retreats somewhat from this position and states that in view of the recent investigations upon the treponema and of its presence in the ovary third-generation transmission may be a possibility It seems therefore, that the discovery of the treponema and of the W R., which were made since the previous edition of his work had been published, had led him to modify his strong view and apparently he had grafted his later view upon the more rigid one he had previously held, without properly integrating them. Hutchinson's eminence in the profession was so great and his knowledge of venereal diseases so extensive that British medicine accepted his views almost without question. George Ogilvie (1897) in a long paper upon the subject, gave a critical survey of the reported cases, drawing attention to the weak points in several of them. In his opinion it was not essential that syphilis should be demonstrated in one or other grandparent as Fournier demanded because it is undoubtedly possible to diagnose congenital syphilis in a parent by signs or symptoms and evidence of syphilis in the grandparent is of corroborative rather than of absolute value, as Ogilvie remarks. With regard to Fournier's and Finger's second postulate, namely that acquired syphilis in the second generation must be excluded, Ogilvie writes It must be granted once and for all that absolutely to exclude acquired syphilis is impossible Common sense and a sound valuation of the probable must step in where absolute proof is impossible. It must be remembered that these words of Ogilvie were written before the discovery of the treponema and of the Wassermann reaction, and while a positive reaction in the father might be taken as evidence of acquired syphilis a negative reaction would have little value because, as is generally recognized, the fathers of syphilitic children, even with a history of a syphilitic infection, frequently have a negative W R. Ogilvie sums up his review in the following words We are told that there is not the slightest evidence of third-generation transmission and, on the other hand, that there are undoubtedly cases in which syphilis was thus transmitted. Both statements are equally unwarranted. The evidence before us furnishes us, if not with absolute proof still with reasonable probability that syphilis may descend to the third generation. Rietschel (1927), in Jadassohn's monograph, refers to a number of positive cases, but he states that hardly any of them satisfy the

conditions set down by Fournier and Finger If all the recorded cases are critically examined, however one cannot doubt he says, that syphilis can be transmitted to the third generation and possibly even to further generations. Its occurrence, we may believe, is not so infrequent but it cannot always be proved in actual practice.

American authorities do not appear to regard third generation syphilis sympathetically holding the view that practically none of the recorded cases satisfies the Fournier and Finger postulates. Stokes writes It is generally conceded that a tendency to constitutional inferiority appears in the children of parents who have severe forms of hereditary syphilis. Those who have inherited syphilis in mild form may if sufficiently treated, give birth to healthy children The Solomons say that while there is some divergence of opinion, the general tendency is to believe that syphilis is not transmissible beyond the second generation, from which they infer that a congenitally syphilitic individual is probably never contagious by the time the age of marriage has been reached On the other hand, Jeans and Cooke (1930) say that *At present we can only speculate* about the possibility of congenital syphilis in the father being transmitted to the third generation The probability of a woman with congenital syphilis transmitting the infection to her offspring depends almost entirely upon the possible duration of the disease in such a woman. We know that a woman with acquired syphilis can give birth to syphilitic children for 20 or more years, and therefore there is no reason why the treponema should not remain transmissible for so long a time in the infected offspring" They add The chain of circumstantial evidence accompanying many of the reputed examples is such as to provide a high degree of probability for this type of transmission.

Kemp and Poole in their article on congenital neurosyphilis were of the opinion that 2 of the 20 mothers in one of their series were themselves congenital syphilitics, and that the family almost certainly represented third generation syphilis. Another American writer W M Sams in reporting a case expresses his belief in the existence of the condition and in the points connected with the diagnosis he refers to the parentage of the child in question which should be undoubted he himself seems to have been the first to stress this point.

In connection with third-generation syphilis a problem sometimes arises as to whether the congenital mother can be reinfected by a syphilitic husband or not. A number of authors have described cases in which a congenital patient appeared to have acquired syphilis and this would seem to be undoubtedly possible. This aspect of infection was discussed by Tarnowsky at the International Congress of Medicine in Paris in 1900 He reported cases of acquired syphilis in congenital patients and suggested the term syphilis binaria for this type of case A number of American writers have concerned themselves with the question of im

munity and reinfections or super infections in syphilis (Chesney Halley and Wasserman, Urbach and Beerman and others)

My own experience having been mainly with congenitally-syphilitic children and their mothers, I have not had many opportunities of attesting the possibility of super infection in a congenitally-syphilitic father or mother My own view is that if a congenital mother is untreated and still has a positive W.R. she would not be liable to reinfection. If on the other hand, as a result of treatment, or possibly by efflux of time, her serological reactions had become negative, I consider it would be possible for her to acquire a second infection. Similarly a congenital father whose serological reactions were negative, might conceivably be susceptible to an acquired infection.

Personal observations

In 1927 in a paper read before the Medical Society for the Study of Venereal Diseases in London, histories were given of 8 families with syphilis in 3 generations and of 3 others in which the sequence was probable or possible. In the first category were included cases in which grandparent, parent (usually the mother) and child all had a positive W R. also cases in which the parent (that is, the second-generation mother) had obvious stigmata of congenital syphilis, such as typical Hutchinsonian teeth, rhagades or interstitial keratitis, from which one concluded that one or both grandparents were syphilitic. On further inquiry in most of these cases I was able to elicit the fact that the grandfather had died in a mental home of paralysis, which was subsequently confirmed to have been general paralysis.

I regard it of extreme importance when a history is taken of a patient, and particularly of a child, that the mother should be herself examined, and inquiry into her family history—parents, brothers and sisters—should be made.

In the second category of probable syphilis in three generations, I included cases in which the mother was obviously a congenital syphilitic and the child might have had the disease in infancy but owing to an imperfect history and absence of blood tests at the time, and a negative W.R. when the child was seen by me, I was unable to be certain of the diagnosis. If the child's early symptoms suggested that it might have suffered from the disease the case was called *probable* whereas if the early symptoms were more vague it would be classified as *possible* A similar grading would apply to stillborn children.

In the 5 years following 1927 my list of families increased from 8 to 16 with syphilis in three generations, from 1 to 6 in which the disease was *probable* in the third generation and from 2 to 7 in which it was *possibly* present and in addition I had come across 2 families in which both parents were congenital syphilitics. This larger group of cases formed

the subject of a presidential address I delivered before the same society in 1933 and the considerable additions which were made during the 5 years I had been on the look-out for such cases would suggest that the condition is not so rare as is commonly thought If such be the case, it may legitimately be asked why other authorities have not recorded similar experiences.

There are probably several answers to this question. First and foremost, I think, is the fact that life is so strenuous to-day that we do not allow ourselves time to do things thoroughly For example, unless a mother were almost blind from corneal nebulae or had a saddle shaped nose or rhagades which could be detected from the other end of the consulting room, how many paediatric physicians or surgeons would take time to investigate such a mother and possibly inquire into her family history when it was her child about whom she had come to seek advice? I have on many occasions seen mothers with obvious stigmata of congenital syphilis which had been missed, doubtless because the physician or surgeon had a definite and usually too large a number of patients to examine. Secondly I had learned to detect finer diagnostic features, such as minor degrees of malformation in the incisors and 6-year-old molars, broadening of the forehead with some widening of the bridge of the nose in the parent which has prompted further inquiry into the personal and family history In this way I was able to elicit information about earlier eye trouble in the mother herself or in one or more of her brothers and sisters, about her mother s obstetric history or possibly her father s death from general paralysis, tabes, aneurysm or heart disease. Thirdly there is the lack of appreciation by clinicians that one negative blood test on mother or child does not necessarily preclude syphilis. Fourthly practically the whole of my experience was gained from patients of the hospital class amongst whom acquired syphilis in the father formerly received rather inadequate treatment, so that the chances of congenital children being born were great Practitioners who treat syphilis in private doubtless get their patients to attend more regularly and oftener so that such patients are less likely to transmit the disease to their offspring

The conclusions which I drew from my observations recorded in 1933—though lacking in absolute proof—were that a congenitally-syphilitic mother who had received no or perhaps only very little antisyphilitic treatment might transmit a severe or florid congenital syphilis to her child even though her husband were healthy The explanation may be that she is a carrier of the treponema in her ovaries or other pelvic organs. On the other hand if she has received some treatment or even if she improves spontaneously she may transmit only a mild form of the disease to her offspring or the child may be only undersized or possibly the effect on the child may be the presence of petit mal mental retardation or some other form of so-called para-syphilis or occult syphilis. This is a

possibility which in my opinion should be borne in mind. *It must also* be remembered that a congenitally-syphilitic mother equally as well as a mother who has acquired the disease in the usual manner may bear healthy children alternately with infected children. I made two further observations in connection with the children of congenitally-syphilitic mothers (1) *that in several of the families it was the second child who was* apparently most markedly affected and (2) that in several of the families the affected child showed involvement of the central nervous system. This might take the form of a typical neurosyphilis (clinical or latent) with a positive spinal fluid, or of an atypical case such as (i) D C (p 291) who had a progressive hydrocephalus with a normal C.S F (ii) L.W (p 289), who had a paretic fluid with granularity of the ventricular ependyma, yet a negative blood W R. (iii) K.T and (iv) S.S both of whom had relapsing cerebrospinal fluids. The former had slightly increased protein and cells with negative W R. Kahn Lange and globulin tests at $3^{5}/_{12}$ years, yet a strongly positive W R. with slightly increased protein, cells, Lange and globulin at $10^{10}/_{12}$ years, and a normal C S F 2 years later whereas the latter is referred to in Table 16 case 14, and Table 32, case 32 (pp 276 402) where it is seen that the C.S.F relapsed twice before becoming negative eventually at the age of 5 years. Further observations upon these two points are needed before we can conclude that they are usual, and not accidental, occurrences. A congenital father appears to be much less likely than is a congenital mother to transmit the disease to his offspring and it is noteworthy as was pointed out in the chapter on neurosyphilis, that mothers with neurosyphilis are much more likely to transmit neurosyphilis to their offspring than are neurosyphilitic fathers. The interested reader is referred to the author s original paper for details of the families referred to but a few of the more interesting families are recorded below

Family 363. The grandmother had 15 pregnancies, including 5 miscarriages. Of 10 living children only 2 are now surviving, of whom the patient s mother is one. The grandmother's W R., at the age of 86, was very strongly positive, but she had no symptoms or signs of the disease. Five years later at 91 she was still hale and hearty and the W R. was practically negative, but the Kahn was positive. The second-generation mother had I.K. from 8 to 17 years of age. She attended Moorfields Eye Hospital and was treated with pills. In 1911 her W R. *was nearly negative and in 1917 quite negative. She had typical Hutchinsonian teeth and corneal opacities, yet when she attended the Children s* Hospital in 1909 and again in 1911 with her daughter (third-generation patient) her congenital syphilis passed unnoticed by the surgeon. The husband s father (second generation) is said to have had syphilis and to have been treated, but was not seen by me. Of 16 pregnancies only 2 children survived. The elder one born 1909 had a rash at 3½ months and was treated with mercury for 4 years, but at 8 years of age the W R. was still positive and in spite of vigorous treatment by injections it did not become negative until the age of 22. Her sister who was born 8 years later had no symptoms and a negative W R. until the age of 15

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This family shows syphilis in three generations, though it is impossible to say whether the mother's congenital syphilis was transmitted to her daughter or whether it was an example of super infection, the second generation mother having been infected by her husband The family also illustrates the interesting point that an individual may have a strongly positive W R. at the age of 86 and appear to be perfectly well with no obvious signs or symptoms of syphilis, and that without treatment the W R. could become negative 5 years later even at that advanced age.

Family 376 The maternal grandmother (first generation) died of locomotor ataxy The mother has typical facies, corneal opacities and positive W R. (second generation). Father no history of syphilis and W R. negative. Married in 1910 Children

1 1911 Girl. No signs or symptoms of syphilis up to 12 years of age but W R. strongly positive at 11 and 12 years of age.
2. 1918. Male. Mentally defective and unable to sit up. W R. strongly positive. Became negative in 1923 but was still very mental when last seen in that year C.S F was not examined.
3 1919 Abortion at 1½ months.
4. 1920. Female. No symptoms in infancy or during the first year W R. negative.
5 1922. Female. Not seen or tested.

This family shows syphilis in three generations, the second-generation mother having very typical syphilitic facies and old interstitial keratitis (see Fig 29) The first child had no signs or symptoms of the disease, but had a positive W R. whereas the second child born after a long interval, was very severely infected and mentally defective

Family 109 The maternal grandmother (first generation) had no symptoms, but was found to have a strongly positive W R. Mother (second generation) had no symptoms, but had a history of slight snuffles. The W R. was very strongly positive during 3 years in spite of much treatment and was persistently positive after 3 more years, making 6 years in all. It was this fact which led me to inquire into the possibility of her having congenital syphilis. The father (second generation) admits no possibility of infection. His W R. and Kahn were negative Married 1920. Children

1 1922. Stillbirth at full term.
2. 1925 Male. Florid congenital syphilis at one month W R. strongly positive but rapidly became negative.
3 1927 Male Born after mother's treatment. No signs or symptoms of the disease during the 3 years he was under observation.
4. 1931 Died in 10 days, ? cause Patient was not seen by me

Family 648 Maternal grandfather (first generation) died of G.P I (verified). He and his wife had 12 or 13 children and only 4 survived

1 1894. Male Said to be well.
2 1896. Male Said to be well. Had I K. aged 36. Married and has 2 healthy children.

3\. 1897 Female (second-generation mother) No early history available His broad, bossed forehead and the right lower canine notched. Nearly all the other teeth are artificial. Married 1920 and when seen in September 1922 her blood was very strongly positive. Twelve years later she developed G.P.I. at the age of 36 Her husband could not be induced to come up for examination. Children

(1) 1921 Male. Small baby—birth weight only 4 lb. No rash or snuffles. Had a double hernia and was under supervision for 6 or 9 months. Seen by me in 1932. Is small but has no signs of congenital syphilis. W.R. and Kahn negative.

(2) 1927 Male. Healthy baby but had a big head. At 3 years had slight jaundice and history of dark urine. Blood count, fragility tests, liver function tests, Van den Berghs reaction and C.S.F. were all examined at another hospital and said to be negative or normal. When seen at Great Ormond Street his blood gave a strongly positive W.R.

4\. 1903. Female Married and has 3 children, all said to be healthy

This case is of interest because it brings out rather clearly the point I have already stressed, that by paying more attention to the parents of our young patients we can often obtain considerable help in diagnosis. This boy had attended hospital on many occasions for treatment, but the suggestive appearance of the mother had apparently not been noted. Owing to her brother recently having developed interstitial keratitis, which be it noted, occurred at the age of 36 years, her family history had been gone into and the mother herself had already been acquainted with the result, but she had not imparted the information to the hospital physician under whose care her little boy had been. One may note further that it is again the second child who shows signs of congenital syphilis, though it is just possible that the older boy who weighed only 4 lb (1·8 kg) at birth, might then have had mild symptoms of congenital syphilis although his W.R. and Kahn were negative by the time he came under our observation (See also under "Congenital General Paralysis," p 306)

Family 422 This family is of interest because it is the only one in which a congenitally-syphilitic father appeared to convey an infection to one or two of his children without the wife ever showing any sign or symptom of syphilis. The paternal grandmother (first generation) had a strongly positive W.R. when seen by us at about 60 years of age. She had been married 8 years before the birth of her first child, who became the second-generation father He is said to have been a healthy baby but had chest trouble. Fourteen years later a girl was born who died of diphtheria at 2½ years of age. The paternal grandfather is said to have been healthy He was a sailor in the mercantile marine, a calling which at that time was a fertile source of syphilis. He is said to have died at the age of 60 from pneumonia. The second-generation father had a big broad head rather suggestive of congenital syphilis. The teeth were bad but not Hutchinsonian. He gave no history of syphilis or of the possibility of having acquired it before marriage His W.R. was strongly positive in 1921 and also on three occasions in 1922. Between these dates he was given 20 injections of sulfarsphenamine and mercury iodide pills. One year later the C.S.F. was negative

in all respects. In 1927 the S.W R. was almost negative and in 1938 the W R. and Kahn were quite negative The mother has never shown any signs or symptoms of the disease, and her blood W R. was negative on many occasions between 1921 and 1938.

This family has already been referred to in the chapter on Transmission (p 51)

In the next two families both parents were congenitally syphilitic

Family 5?3 The father was born in 1899. There is no available history of infancy and childhood but at the age of 13 he was treated for his eyes, and apparently his sight had never been normal, though he was able to work until he was 21 years of age. At the age of 30 he was seen by Dr (now Sir Francis) Walshe of University College Hospital, who reported that "his right pupil was dilated and inactive to light choroido-retinitis and patches of exudate in the lens were present. Knee and ankle jerks were not obtained others were present." Dr Archibald Gray noticed at the same time that the bridge of the nose was depressed and the central incisors typically Hutchinsonian. His W R. was positive and he was given three injections of N.A.B I examined him a few weeks later and found him to be obviously a congenital syphilitic and his W R. was strongly positive. His father had died of pneumonia at 34 years of age and no history could be obtained about his mother except that she had remarried. The second-generation mother was born in 1900, snuffled in infancy and was said to have been almost blind from birth. She attended Moorfields Eye Hospital every week. In September 1928 at the University College Obstetric Hospital her W R. was found to be negative. She was seen by Dr Gray for the first time two months later when she was 8 months pregnant. He found opacities of both corneae, irregularity of the left pupil, a depressed nasal bridge and Hutchinsonian central incisors. Clinically the case was obviously one of congenital syphilis, but the W R. taken at that time was negative as it was also a week later after a provocative injection of N.A B. I saw the patient 4 months later with her child. She was obviously a congenital syphilitic, although her W R. was again negative. The child, born in December 1928 is said to have snuffled at birth, but had no rash. The cord blood was negative When seen by me at 3½ months, there were no symptoms and the W R. and Kahn were negative Eight months later when he was about a year old, he was still free from symptoms of congenital syphilis. The mother was at that time again 4 months pregnant, but the subsequent history could not be ascertained because the family moved into the provinces.

This case is of interest inasmuch as both parents were undoubtedly congenital syphilitics and presumably both had been treated on account of eye trouble. This doubtless explains why the first child that was born to them gave a negative serological reaction. If it was infected at all (which is just possible, as it is said to have snuffled at birth), the infection must have been a very mild one.

Family 71 Both parents were congenital syphilitics, the father having been treated by me when a child the mother was untreated The paternal grandfather born 1880, was a steward in the Mercantile Marine and he may have contracted syphilis on one of his voyages. In 1932 he was said to have been well.

The paternal grandmother was born in 1881 and married in 1903 Her W R in May 1915 was strongly positive She had no symptoms between 1915 and 1932. Their family was as follows

1 and 2. Stillbirths.

3. 1906. Male, "second-generation father He snuffled in infancy and had periostitis of the tibia at 9 years for which he attended Great Ormond Street. His W R. was then very strongly positive. It became negative as a result of treatment in 1918–19 and was still negative in 1927 In 1932 he appeared to be quite well.

4. 1909. Female. No symptoms in infancy or until puberty In 1929 she is said to have had a "rheumatic heart. Her W R. and Kahn were "doubtful.

5. 1911 Male. No infantile symptoms. 1915 W.R. weak positive 1929 not strong ? rheumatic.

6. 1913 Stillbirth.

7 1915 Male. No infantile symptoms. Developed rheumatism at 4 years and died of valvular disease of the heart.

8. 1919. Male. No infantile symptoms. 1929 ? rheumatic. Enlarged glands in the groins. W R. and Kahn negative 1929.

Second-generation mother born 1907 Her father died at 39 of "consumption and her mother at 41 of ? cancer At the age of 21 she was in a general hospital in London for tuberculous kidney which was removed. It was then recognized that she had typical Hutchinsonian teeth and her W R. was found to be positive. No antisyphilitic treatment was given or even suggested. In June 1930 she married patient No. 3 referred to above, who had been treated for and was presumably cured of his congenital syphilis. A baby was born in December 1931 who appeared healthy except for a left inguinal hernia. For this he was brought to Great Ormond Street Hospital where the almoner recognizing the name, upon inquiry found that the child's father had been originally my patient in 1915 Knowing that I should be interested to see this child she brought him to me. He was then 2 months old and showed no symptoms or signs of congenital syphilis. His mother's blood was examined and found to be strongly positive but the child's blood was not examined until he was 6 months old. It was then strongly positive, so it was obvious the child was suffering from latent congenital syphilis as there were no symptoms of the disease present. X-rays of the long bones showed evidence of old periostitis especially of the tibiae. In October of that year at the age of 10 months, the W.R. was still strongly positive and the C.S.F weakly positive.

This case is perhaps one of the most, if not the most, interesting in the series, because the father had been treated for congenital syphilis and he was apparently quite well at the time he married. The wife had never had any treatment and it would appear that her untreated congenital syphilis was transmitted to the child. The case also raises the important question whether if a woman is accidentally discovered to have congenital syphilis, she should be advised that treatment was necessary for her even though she may have come under observation for a totally unassociated condition, as this patient did.

In my opinion the patient's doctor should always be informed if congenital syphilis has been discovered in his or her patient, or if she has no

doctor then I think the patient herself if of age should be advised to have treatment. If under age then the parents should be informed and recommended to have treatment given to their child.

Between 1933 and 1939 I came across 12 more similar families where there was syphilis in three generations or where the children of the third generation had probable or possible (B or C) syphilitic manifestations. Two of these congenital mothers had children who were probably not syphilitic, but as they had had only one and two children respectively in 1939 further information about them which unfortunately owing to the war was unobtainable, might have led to the detection of subsequent syphilitic children Two other mothers, whose own mother suffered from tabes, had two children and one child respectively The elder daughter had two children, the first being well and the second being possibly syphilitic (a C case) He had no infantile symptoms, but suffered with fits since a fall at the age of 9 months. His blood and spinal fluid both gave negative tests at the age of 5 years. The younger daughter had one child, who was brought to Great Ormond Street and seen by Dr Reginald Lightwood who diagnosed amyotonia congenita at the age of *8 months. The child's W. R. was then negative but as the mother's* S W R was weakly positive the child in view of his clinical condition might be regarded as a possible congenital syphilitic (a C case)

Among the families with syphilis in three generations encountered the signs and symptoms exhibited by the mother which prompted inquiry into the possible presence of congenital syphilis in her may be summarized as follows

Typical or suggestive *Hutchinsonian teeth 15 cases.*
Facies, including rhagades squint and unequal pupils and pharyngeal scarring 10 cases.
Persistently positive W R. 6 cases.
Signs of old keratitis 3 cases.
Suggestive history of the mother's mother or sibs 6 cases
Mother's own history of Raynaud's syndrome and of interstitial keratitis *1 case, and*
One died of congenital G P I

It should be mentioned too that once suspicion had been aroused more cases of interstitial keratitis were disclosed, but these had apparently almost entirely cleared up

This summary illustrates the importance of recognizing the minor degrees of Hutchinsonian characteristics of the teeth and of bearing in mind the other *stigmata and possible indications of congenital syphilis in* mothers which may thus give a possible clue to the nature of physical and mental defects, malformations and obscure conditions in their children.

TABLE 31

Details of 42 Families with probable Syphilis in Three Generations

Total number of families showing "probable" or "possible" syphilis in three generations	= 42
Total pregnancies	= 157 including 3 twins
Average per family	= 3·74
Survivors	= 92 (? 94)
Average per family	= 2·2
Children	
Well	= 45 (12 born after mother's treatment)
Result unknown	= 9
Congenitally syphilitic	= 19 } 38 congenital syphilitics
Congenitally neurosyphilitic	= 6 + 3 possibly neurosyphilitic }
"B" or "C" cases living	= 9[1]
"B" or "C" cases died	= 21
Died (unknown cause)	= 3
Premature births or miscarriages	= 35 (most of these were probably syphilitic)

[1] These include such lesions as epilepsy, mitral valve lesions, bleeder and case with amyotonia congenita.

The deaths may be summarised as follow:

Premature births or miscarriages (mostly syphilitic)	= 35
"B" and "C" cases, probably from syphilis	= 21
? cause	= 3
Arsenical dermatitis at 4 years	=
Empyema and syphilitic lung at 8½ years	= 1
Total	61

A few others died of conditions unassociated with syphilis.

Summary

My own view on third generation syphilis is that during the 30 years that I was particularly interested in this disease, congenital syphilis in the mother played a not inconsiderable part. I think it is certainly possible for a woman with untreated congenital syphilis to have congenitally-syphilitic children by a healthy husband and furthermore that if the children are not obviously infected by the treponema, their developing tissues and organs may be adversely affected by the maternal syphilis. In the last event the child's W. R. would be found negative and antisyphilitic treatment carried out after birth would be of no benefit to the patient. To this condition the name "para-syphilis" or "occult syphilis" might be given.

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The above list of references makes no claim to being exhaustive but gives both sides of the picture.

CHAPTER 10

FAMILIAL SUSCEPTIBILITY OF INDIVIDUAL TISSUES TO SYPHILITIC INVASION

In Chapter 8 it was stated that neurosyphilis may not infrequently be observed in one parent and a child and, more rarely in both parents and a child. Such occurrences have led to the long-disputed problem of neurotropic versus dermotropic treponemata. The subject was discussed at a meeting of French physicians and syphilologists (1926) after the presentation of a paper by Guillain, Périsson and Thévenard on neurosyphilis in three members of a family The parents gave no history of syphilis and had received no treatment, yet on examination they both showed signs of tabes dorsalis. Their child, a boy of 4, had dilated and unequal pupils the Argyll-Robertson phenomenon and a positive W R. Three similar family records were given by the authors of the paper The ensuing discussion brought out various points of view but most of the speakers disagreed that there were two different treponemata, neurotropic and dermotropic. Guillain, in replying to the debate, said he did not mean to infer that there were two different diseases, the one solely neurotropic, the other exclusively dermotropic, but he believed that there were certain treponemata which had acquired a particular pathogenicity for the nervous system, that property whether called virulence or organotropism being possibly dependent upon different causes. Flandin (1926) writing also against the duality of treponemata, suggested that these organisms might acquire a selective affinity for the nervous system, but, he added the same might be said about other viscera, for we not infrequently see conjugal or familial syphilis of the aorta, liver and possibly other organs He gave as instances (1) aortic syphilis in two brothers and the wife of one of them (2) conjugal aortic syphilis (3) conjugal syphilis with joint lesions in the husband and gastro-duodenal symptoms in the wife, all benefited by antisyphilitic treatment (4) syphilitic aortitis in a father and son. Flandin was of the opinion that these familial instances of elective localization were not infrequent. Two explanations are possible, he says (1) that certain treponemata have a selective affinity for a particular tissue or (2) that it is the soil which determines the localization. He dismisses the former on morphological and experimental grounds and so believes in the soil or rather in the adaptation of a given treponema to the soil which

received it. This reaction between the seed and the soil is a view I have held for many years, and it is important to remember that the soil goes back through the genes to innumerable generations, in one or more of which syphilis may have been present, so heredity and immunity may play a part in the process

Personal Investigations

We present our results under the following headings

1 Absence of infantile symptoms of congenital syphilis.
2. Latent syphilis when patients were first seen. It is possible that a familial immunity may play a part in 1 and 2.
3 Teeth.
4. Large, bossed head.
5 Otorrhoea.
6 Deafness.
7 Recurrent parotitis.
8 Palatal ulceration
9. Bleeding from the nose in infancy
10 Cervical adenitis.
11 Ischaemic disturbances (Raynaud like syndrome) in fingers
12 Interstitial keratitis and other eye lesions.
13 Neurosyphilis.
14 Familial similarities in reactions to treatment

These are not all of the same importance or interest Some, for example 12 13 and 14 comprise many more patients than most of the other groups, whilst others, for example 4 5 9 and 10 are common symptoms of congenital syphilis and would therefore not be unexpected in sibs

Taking the categories seriatim

1 In 16 of our families 2 sibs in each and in 4 additional families 3 sibs in each had no infantile symptoms and of these patients, 8 pairs and 1 set of 3 sibs were *latent syphilitics* when first seen by us

2. In all latent sibs were seen in 12 families, 11 pairs and 1 trio in cluding those mentioned in 1

3 Two pairs of sibs had typical Hutchinson and Moon teeth 6 pairs and 1 trio had less marked Hutchinsonian teeth (H2 or H1) Two pairs of sibs had mulberry molars with the characteristic crateriform decay In 5 pairs of sibs the teeth were good

4. In 4 families, 2 members had large bossed heads a father and daughter and a mother and son all of them congenital syphilitics there were pairs of sibs with bossed heads in the 2 other families. Heredity or familial likeness might have been the cause of this particular characteristic

5 6. Three pairs of sibs suffered from otorrhoea Two other pairs of

sibs suffered from deafness of internal-ear type: 2 were sisters, congenital syphilitic mothers who have been previously referred to (see p 368) the other pair were brothers, who also had choroiditis and were blind in one eye. One of them suffered from interstitial keratitis, as did also a mentally-defective sister

7 A brother and sister had recurrent attacks of parotitis (see p 159)

8 A congenitally-syphilitic son had an ulcer on the palate at 3 months the mother also a congenital syphilitic, had an ulcerated mouth at the age of 21

9. A brother and a sister had bleeding from the nose in infancy

10 Two sisters, who had no infantile symptoms, afterwards developed cervical adenitis, which was so marked in one of them that the diagnosis of lymphadenoma was considered in her case.

11 Two infants who at about the same age (3 weeks old), had ischaemic changes in the terminal portions of the fourth and fifth digits of the right hand with commencing gangrene. The mother of the children was herself congenitally syphilitic but the children were not obviously so and they may perhaps be looked upon as suffering from occult syphilis of the third generation.

12. In ocular lesions occurring in members of the same family interstitial keratitis easily takes the first place, as the condition was present in 13 of our families in the following combinations brother and sister 4 times half brother and sister once 2 brothers, twice 2 sisters, 3 times 3 sisters, once in a congenitally-syphilitic mother and daughter and a congenitally syphilitic aunt and niece, each once. Further points of interest in these patients were The half brother and sister who had interstitial keratitis at the ages of 11 and 7 also had periostitis of the tibia at 10 and 8 years of age respectively A brother and sister each of whom had a mild attack of interstitial keratitis (at 8 and 9 years respectively) both had latent congenital neurosyphilis with a Wassermann-fast cerebrospinal fluid and blood at 14 years of age, and both had typical Hutchinson and Moon teeth. A mother who started her congenital general paresis at 35 had two brothers both of whom began to suffer from interstitial keratitis after they were 30 years old. A family of 3 sisters, who had interstitial keratitis at 2½ 9 and 14 years respectively all subsequently showed slight corneal opacities, and were all mentally retarded. In the case of a mother and daughter who both had interstitial keratitis the mother's teeth were typically Hutchinsonian whereas the daughter's were normal. Other ocular lesions in sibs were choroidal atrophy with secondary optic atrophy in a young brother and sister interstitial keratitis in one boy and choroido-retinitis with possibly some vitreous opacities in the brother and 2 sisters, both with a squint, one of whom had *Keratitis punctata profunda* and a year later a relapse in that eye with a corneal ulcer whereas the other had old choroiditis in the right eye and an inflamed left eye, which was hazy at

the age of 6 years There were doubtless further cases in which slighter manifestations of choroido-retinitis were present in sibs but which were not recorded or were overlooked

13 There were 35 families in which two or more of the members were the victims of neurosyphilis

A 8 in which two sibs had neurosyphilis
B 11 in which the father and son (4) or daughter (7) were affected
C 3 in which the mother and son and
8 in which mother and daughter were affected
D 3 in which grandparents and grandchild had neurosyphilis, one family showing neurosyphilis in 3 generations and lastly
E. 2 families in which both parents and one child had neurosyphilis.

14. We come lastly to similarities of reactions to treatment in two members of a family The numbers in each category are small so they may have been accidental, but as the incidents were recorded at the time it may be of interest to relate them

1 There were 5 pairs of patients who exhibited Jarisch Herxheimer reactions 2 mothers with their sons 2 mothers and their daughters, and a brother and sister

One mother had headache and dizziness after neo-arsphenamine, the son had an immediate reaction with generalized erythema. Another mother was sick and giddy her boy had sickness and diarrhoea. Two mothers and daughters all had sickness and a rash after each injection of arsenic compound

2 Among patients exhibiting familial skin lesions were two sisters one of whom was very susceptible to arsenic, while the other was less prone to having a rash but in addition suffered from two attacks of herpes. *These two girls reacted to both arsenic and bismuth injections* A mother developed a bad attack of arsenical dermatitis after taking stovarsol, while her child, aged 4 weeks, had diarrhoea and a rash while taking the drug Both patients responded to treatment, and it is noteworthy that the blood reactions (W R. and Kahn) behaved similarly for they were negative in mother and infant when examined 7 and 14 months, after being strongly positive at the first test.

3 Jaundice after injections of arsphenamines is rare in congenital syphilis (see p 426) and when it appears to have occurred a more thorough inquiry may establish or suggest the possibility of the child's syphilis being acquired and not congenital We had several such cases among our patients one which almost certainly suffered from acquired syphilis was sick after each injection whether intramuscular or intravenous, and became mildly jaundiced after one injection. The father's injections of arsphenamine at another hospital had to be stopped on account of jaundice and courses of bismoxyl substituted for them.

TABLE 32

Thirty-five Families in which two or more Members had Neurosyphilis

Class A. 8 families with sibs affected

Name age and sex	Manifest (M.) or Latent (L.)	Clinical manifestations	C.S.F. W.R. at start	C.S.F. W.R. at termination	Outcome
1. J.K. ♂ 11/12	M.	? T.B. meningitis, hemiplegia.	4444	—	Died. P.M. syphilitic panarteritis of the carotid and mid. cerebr. arts.
R.K. ♂ 1 4/12	M.	Hemiplegia, deaf, polio-encephalitis.	4444 when examined yrs. later	Neg.	Alive and well, except for paralysed arm, in 939
2. T.M. ♂ [illegible]/12	L.	None.	4444	Neg. in yr.	Well at 8½ yrs.
W.M. ♂ 1 11/12	M.	Fits; hemiplegia.	4444	Neg. in 3½ yrs.	Alive. M.D. paralysed at ½ yrs.
3. F.T. ♂ 7	M.	G.P.I. (seen at another hospital)	—	—	His S.W.R. was found strongly pos. by us at the age of 7 yrs. Died G.P.I. at 22 yrs.
J.T. ♂ 3½	M.	G.P.I.	4444	Neg. in 6 yrs.	Well at 18 yrs. Had been in the Army
4. A.G. ♂ 8 1/12	L.	None (I.K. later)	4444	4444	Defaulted at 4 yrs. after much treatment, including malaria
E.G. ♀ 9 2/12	L.	(I.K.)	44	4443	Defaulted 4 yrs. after some treatment
5. A.P. ♂ ½	M.	Hydrocephalus and signs of meningitis.	Grade Prot. and cells + W.R. neg.	—	Died from an accident at ½ yrs.
D.P. ♀ 6	L.	Later unequal pupils, R. inactive.	44	Neg. in 1 4/11 yrs.	Pupils small, R. inactive 3 yrs.
6. R.S. ♂ 8½	M.	Fits at 4½ yrs. (I.K. at 5 yrs.)	4444	—	Died G.P.I. at 3 12 yrs.
K.S. ♀ 6½	L.?	Precocious; swears. L. pupil slightly > R.	4444	Neg. in 4 yrs.	Well treated and well at 3½ yrs.
7. G.W. ♂ 8 11/12	M.	M.D. R. pupil > L.	44	—	M.D. and alive at 14½ yrs. G.P.I.
G.W. ♀ —	M.	I.K. and meningitis.	Seen at another hospital		
8. E.H. ♀ 4 1/12	M.?	Slightly mongoloid in appearance	30.	Neg. in 3 mths.	Alive and well at ½ yrs.
M.H. ♀ 2½	L.?	? slightly M.D. fits of temper	44	Neg. in 7 mths.	Still troublesome at times at age 9½ yrs.
Class B. families in which the father and child had neurosyphilis					
9. N.B. ♂ 3	L.?	Gait (?) at 3 yrs., syphilis not suspected (I.K. at yrs.).	Grade Prot. + & Lange.	—	Defaulted at 14 yrs.
Father	M.	T. dorsalis.	Seen at another hospital.		
10. R.W. ♂ 25	M.	Early tabes at 35 yrs. Later taboparesis.	Seen here.		Taboparesis; still alive at 48 yrs. after much treatment.
Father	M.	Taboparesis.	Do.		Taboparesis; died aged yrs.

Daughter of R.W. is well at age yrs.
A younger brother and sister of R.W. died aged 4 yrs. paralysed and yrs. blind and respectively

TABLE 32—*Class B* (continued)

Name age and sex	*Manifest (M) or Latent (L)*	*Clinical manifestations*	*C.S.F. W.R. at start*	*C.S.F. W.R. at termination*	*Outcome*
11 F ♂ —	M	G.P.I. (? congenital).	Seen elsewhere		Died G.P.I. at 38 yrs. A brother died of [illegible].
Father	M	Paralytic prob. G.P.I.	Do.		Died, probably G.P.I.
12. N.H. ♂ $2^{1}/_{12}$	M	M.D. Hydrocephalus unable to walk or talk	Not examined: was in home from 5 yrs. till death.		Died at 7½ yrs. cong. G.P.I. or meningo-vascular syphilis.
Father	M	G.P.I.			*Died of "paralysis of the brain."*
3 earlier children died from convulsions in infancy					
13. Mrs. A 35	M	Congenital G.P.I. at 36 yrs.	Examined elsewhere		Treated: alive and well at 54 yrs.
Father	M	G.P.I.	Do.		Died G.P.I. at 59 yrs.
Patient [illegible] brothers had late [illegible]—in the fourth decade of life					
14 D.W. 9½	L	Periostitis of tibia	++	Neg. in 9 mths.	Defaulted at 3½ yrs.
Father	M	G.P.I.	++	—	I[illegible] mental hospital. Died G.P.I. at 44 yrs.
There were 5 other children, [illegible] elder and 4 younger than the patient D.W., and 3 miscarriages, but no known case of syphilis among them. Tw[illegible] died young.					
15 D.H. ♀ [illegible]	L (?)	Hydrocephalus and bossed, square head.	++++ at [illegible] yrs.	Neg. at 4½ yrs.	Well at 10 yrs.
Father	M	Tabes dorsalis at 48 yrs.	Being treated elsewhere		
There were 5 other children before patient D.H. One lived only [illegible] hours. Of the other 4 none had any symptoms of cong. syp. or of neurosyp., [illegible] had neg. blood tests [illegible] had pos. blood tests.					
16 V.H. 5	M	M.D. Unequal and fixed pupils, [illegible] teeth	—	L.P. failed.	I[illegible] in an institution
Father	M	Probably G.P.I.	No blood or C.S.F. ex[illegible] carried out		Died at 38 yrs. (prob.) G.P.I.
An illegitimate daughter of the patient V.H. had [illegible] neg. blood test on 7 occasions and [illegible] neg. spinal test and was w[illegible] at 7 years of age					
17 D.B. 7	M	Spastic limbs. Squint	++++ at 7 yrs.	++++ [illegible]	Still al[illegible] ([illegible]) but bed-ridden at [illegible] yrs. Since died.
Father	M	G.P.I.	Treated [illegible] where		Was still alive (N[illegible] [illegible]).
18 F.P. [illegible]	L	Infantile symptoms of congenital syphilis	++ at 7 mths.	Neg. at [illegible] yrs.	Well at [illegible] yrs. [illegible] then defaulted
Father	M	G.P.I.	++++	—	Attended hospital for nerv[illegible] diseases for 3 yrs. then defaulted
19 J.T. [illegible]	M ( )	Hydrocephalus, with infantile glaucoma	+3● at 8 yrs. after much tr[illegible] when first seen by us	Neg. at $9^{1}/_{12}$ yrs.	Blind School patient [illegible] improved so much that patient [illegible] able to go home
Father	M	G.P.I.	—	—	W[illegible] treated [illegible] malaria, etc., and cured in 3 yrs.

Class C [illegible] *families in which the mother and [illegible] child (children in [illegible] are) had neurosyphilis*

20 W.K. ♂ [illegible]	M	Mongol	++	[illegible] after 9 yrs. treatment	Defaulted at 4½ yrs.
Mother	M	Argyll Robertson pupils	[illegible] [illegible] elsewhere		Died tabes dorsalis at [illegible] yrs.
An older [illegible] child died of [illegible] at [illegible] mths.					

TABLE 32—*Class C* (continued)

Name age and sex	*Manifest (M.) or Latent (L.)*	*Clinical manifestations*	*C.S.F.*		*Outcome*
			W.R. at start	*W.R. at termination*	
21 D.P. ♂ $7^{11}/_{12}$	M.	Backward, emotional, slurred speech, fixed pupils.	4 3 o.	—	G.P.I. Died at 8½ yrs jaundice empyema. Probably syphilitic dis. of lung
Mother	M.	G.P.I., probably congenital.	Treated elsewhere.		Died G.P.I. at 28 yrs
Mother had misc. before patient and boy 6 mths. before she died. H. had pos. B.W.R. but neg. C.S.F.					
22 R.B. ♂ $8^{?}/_{12}$	M.	Headaches, etc., G.P.I.	4 4 4 4. at 8½ yrs.	4 o. at 9½ yrs. after 6 intracisternal injections.	Died at 4½ yrs. G.P.I.
Mother	M.	G.P.I.	Treated elsewhere.		Died G.P.I. at 43 yrs.
3 other children died young of fits.					
23 J.R. ♀ $2^{2}/_{12}$	L.	(Condyloma.)	4 4 4 o. at $2^{3}/_{12}$ yrs.	Neg. at 6 yrs.	Well t yrs. after much treatment. War
Mother	M.	G.P.I.	Treated elsewhere. 4 4 4 4 at 34.		Died G.P.I. at 37 yrs
3 other children; older than pt. had latent sy. but not neurosy. the other 2, born after treatment of mother were W.R. neg.					
24 H.R. ♀ 6½ mths.	L (?)	Hydrocephalus, big scalp veins, alopecia.	4 4.	—	Died at 7½ mths. Basal meningitis, esp. at Sylv. fissure.
Mother	M.	Headache, tremor (cong. sy. mother).	4 4 4 4. at 27 yrs.	—	Defaulted at 27 yrs ? G.P.I.
3 misc. other children born after mother treatment—not infected					
25 M.W. ♀ $7^{11}/_{12}$	M.	Fits, unequal pupils, hyperreflexia.	4 4 4 4. at $8^{1}/_{12}$ yrs	4 4 o o. at $8^{1}/_{12}$ yrs	G.P.I. Still had fits at 7 yrs.
Mother	M.	G.P.I.	Treated elsewhere		Died G.P.I. at 44 yrs
26 E.G. ♀ 9½	M.	G.P.I. (congenital).	4 4 4 4. at 9½ yrs	Neg. at 2 yrs. Blood also neg.	Well treated, including malaria. Died G.P.I. at 5½ yrs.
Mother	M.	G.P.I.	Treated elsewhere		Died G.P.I. at 38 yrs
2 later children were not infected, though mother had no treatment					
27 A.B. ♀ $3^{?}/_{12}$	M. (?)	No symptoms, except laryngeal stridor	4 4 at $3^{2}/_{12}$ yrs	Slightly pos. (o.) at $3^{2}/_{12}$ yrs	M.D. Had to be placed in home at 5 yrs. Had malarial treatment
Mother	M.	G.P.I.	4 4	—	Died G.P.I. at 42 yrs
later children born after mother treatment were not infected.					
28 R.H. ♀ 4 12	L.	(Skin lesions on legs.)	4 4 4 4. at 4½ yrs	Neg. at $7/_{12}$ yrs	Well treated, including malaria. Last seen at 7 yrs. then well, but very undersized
Mother	M.	G.P.I.	4 4	—	9 yrs. in mental hosp. Died G.P.I. at 56 yrs
4 other children, the pt. R.H. being the middle one of the 5. Mother had inadequate treatment during her first pregnancy but the child born was uninfected. The second, third and fifth children died in infancy the outcome of frank cong. sy. There was no known neurosy. except in the case of R.H.					
29 N.S. ♀	M.	Paresis L. arm and leg. Diagnosed as poliomyelitis	4 4 4 4 at	Neg. after 7 mths.	Recovered use of arm and leg and ill at 4½ yrs when last seen
Mother	M.	h. l. dysgraph. Slight Romberg	Treated elsewhere		early congenital tab-

TABLE 32—*Class C* (continued)

Name age and sex	*Manifest (M.) or Latent (L.)*	*Clinical manifestations*	*C.S.F.* *W.R. at start*	*C.S.F.* *W.R. at termination*	*Outcome*
30 O.T. ♀ 3 10/12	L.	Latent sy. when seen by us.	++++	Neg. at 5 yrs.	Well at 26 yrs.
B.T. ♀ 1½	L.	Do.	++o.o.	Neg. at 3 yrs.	Well at 24 yrs.
K.T. ♀ ½	L.	Frank cong. sy.	++++	Neg. at 1 mths.	Well at 23 yrs.
Mother	M.	Developed G.P.I.	++++	Neg.	G.P.I. treated and cured.

Class D. 3 families with grandparent and grandchild affected with neurosyphilis

31 B.R. 2 8/12	L.	Latent sy. and latent neurosy.	++++	Neg. in 3½ yrs.	Last seen at 19 yrs.—no symptoms of any kind. (War)
L.R. ♂ 5½	L.	Haemoglobinuria and latent neurosy.	++ .o at 5½ yrs.	Neg. at 6½ yrs.	Well at 21 yrs. (War)

There was another son with latent cong. sy. but not neurosy. Also an older son (first pregnancy) with neg. S.W.R. at 4½ yrs. who is said to have had petit-mal at 5 yrs. after fall at 2 yrs. of age. No C.S.F. examination made.

Mother	L.(?)	Cong. sy. ptosis and external squint. The neurosy. was passed	+ o.o. at 48 yrs. after much tr.	—	Well at 5 yrs. but S.W.R. still strongly positive. (War)

The mother was congenital syphilitic and neurosyphilitic. Her first husband died of G.P.I. 4 yrs. after marriage, no children. Her second husband, father of all the children, is healthy and has negative W.R.

Grandfather	M.	G.P.I.	Treated elsewhere.		Died G.P.I. at 45 yrs.
32 S.B. 5/12	M.(?)	Nystagmus at 5 mths. slight hydrocephalus	Neg. at start. Pos. at [illegible]/12 relapsed again at 3½.	Finally neg. at 5 yrs.	Well and apparently quite healthy at [illegible] yrs.
Mother	L.	Cong. sy. appearance but not manifest neurosy.	Not examined.		Appeared well at 4 yrs.
Grandfather	M.	G.P.I.	Treated elsewhere		Died G.P.I. at 47 yrs.
33 W.S. ♂ 2 4/12	M.	Argent. Fits at 5 mths.	Not tested	—	Unknown. Transferred elsewhere on acct. of distance from the Children's Hospital

An older girl was [illegible] congenital but not manifestly neurosyphilitic. Then after W.S. an abortion, then non-infected child.

Mother	L.	Typical cong. sy. facies and evidence of old I.K.	Not examined		Not seen since 9 [illegible]
Grandmother	M.	Tabes dorsalis	Treated elsewhere		Died of tabes dorsalis

Class E. [illegible] families with both parents and child with neurosyphilis

34 D.H. ♂ 9 4/12	M.	Falling forward in the dark. Pupils unequal and irregular. Primary opt. atrophy	+++o. at 9 4/12 yrs.	Neg. at [illegible]/12 yrs. also S.W.R.	Cong. T.D. almost blind but working at the Blind School at 24 yrs.
Father	M.	G.P.I.	Treated elsewhere		G.P.I. Died pneumonia at 38 yrs.
Mother	M.	G.P.I.	Do.	Neg.	G.P.I. Still alive after much treatment at 3[illegible] yrs., but [illegible] and in an institution at 4[illegible] yrs.

4 other children, 1 older 3 younger than patient, all had neg. blood tests and appeared well.

TABLE 32—*Class E* (continued)

Name, age and sex	*Manifest (M.) or Latent (L.)*	*Clinical manifestations*	*C.S.F.*		*Outcome*
			W.R. at start	*W.R. at termination*	
35. E.P. ♀ $8^4/_{12}$	L.	(Infantile symptoms of cong. sy.)	++++	W.R. fast at $3\frac{1}{2}$ yrs.	Pt. treated in the Kettering hypertherm by M. A. J. King in 1939. At $3\frac{1}{2}$ yrs. only sign of nervous disorder, pupils fail to react to L. and A. (1940.)
Father	M.	Tabes dorsalis at 34 yrs.	++ at 34	—	Said to be well at 41 yrs.
Mother	M.	A.-R. pupils and some loss of sensation to pain at 39 yrs.	Refused L.P.	—	Refused further treatment at 41 yrs.

There was one other girl, $4\frac{1}{2}$ yrs. older than E.P., who had no infantile or later symptoms and was W.R. negative at 3 yrs. A child born 14 mths. after E.P. died in 4 hrs. and is stated to have had large liver.

Notes.

1. In family 30, class C, there were 3 sibs with latent neurosyphilis and the mother developed general paresis under observation. All the patients made good recoveries.
2. In family 3, class D, congenital mother with neurosyphilis had son and daughter with latent neurosyphilis.
3. In the 35 families whose records are given above, there were but 6 known cases of neurosyphilis among the grandparents, for very few of their histories were ascertainable. On the other hand, there were 26 cases of neurosyphilis (13 fathers and 13 mothers) among the parents, and 39 cases of neurosyphilis (18 boys and 21 girls) among the patients of the third generation.

4. In one family we had two treatment fatalities, which may have been due to coincidence or to familial susceptibility to arsenicals. A boy aged 10 years died from encephalitis 5 days after the fourth injection of neoarsphenamine. His sister, aged 2 months, was treated first with sulfarsphenamine and at 4 months with stovarsol. After 18 days on stovarsol she developed diarrhoea and sickness, which persisted till death 10 days later.

5. With regard to similarity in response to treatment, in addition to the mother and infant already mentioned who had dermatitis and speedily gave negative blood reactions, we had 3 other families in which two sisters (twice) responded rapidly to treatment and in the third family the mother, son and daughter responded well. It may be said of these cases that the infection may have been a mild one—a nearly burnt-out syphilis—and that the similarity of response was due to the mild nature of the infection and not to familial similarity of tissue. The opposite condition, slow response to treatment, was seen in 2 families. In the one, a brother and sister, aged respectively $9^8/_{12}$ and $6^{11}/_{12}$ years, both took nearly 5 years (after $2\frac{1}{2}$ years' treatment with arsenicals and mercury in each case) to reverse the blood reaction. In the other family, 4 children, 3 girls and a boy, were slow in responding to treatment (4 to 5 years). It may be coincidence that 3 of them had no infantile symptoms of congenital syphilis and were latent syphilitics when their bloods were routinely examined at $7\frac{1}{2}$, $5^{11}/_{12}$ and $3^{11}/_{12}$ years respectively, but the interesting facts were as they

are related above All the children in this family were of the red haired auburn type and the similarity of the reaction between the seed and the soil may have been due to the special adaptability of the treponema to the tissues. It is also worthy of note that none of these 4 positive children suffered from neurosyphilis.

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CHAPTER 11

THE DIAGNOSIS AND PROGNOSIS OF CONGENITAL SYPHILIS

A CONSIDERABLE change has been effected in the diagnosis and prognosis of congenital syphilis during the last 25 or 30 years slowly at first from the effects of arsphenamine and bismuth treatment of parents and patients, and the prophylactic treatment of expectant mothers and later more rapidly since the introduction of penicillin as a therapeutic agent In consequence, diagnosis of the disease in infants has become much more difficult for two reasons. Firstly the reduction in the severity of the symptoms in these children and secondly the very real reduction in the prevalence of congenital syphilis. This has resulted in the teaching at least in Britain, that the disease hardly exists here and therefore need no longer be considered. I think there is a real danger in this state of complacency or false sense of security

At the end of the nineteenth century down to the outbreak of the first world war frank congenital syphilis was usually easily diagnosable from the snuffles, rash, lesions of the long bones splenomegaly and the general conditions of the patient. Admittedly by relying upon clinical sense alone mistakes were made by missing congenital syphilis when it was present or diagnosing it when it was absent. With the discovery of the *T pallidum* and of the serological reactions diagnosis should have been greatly simplified. But was it so in actual practice? I saw many patients, both during the first world war and after in whom syphilis had obviously been diagnosed by the fact that they had been treated with the time-honoured grey powders or mercury ointment, yet the diagnosis had not been confirmed by a W R. or an X ray examination of the limbs. To make matters worse there was virtually no follow-up in those days so that the infants were given perhaps 2 or 3 months treatment and were then allowed to default. During the war years 1914–1918 this was excusable but this state of affairs persisted into the 1920 s, physicians and surgeons relying on their clinical sense alone, which was often quite correct, but for treatment they trusted to the outmoded mercury even when given the option of arsphenamine injections for their patients. The result was that in subsequent years many patients returned to hospital with the symptoms of late congenital syphilis, often of the central nervous system.

In the year 1952 doctors in three widely separated parts of the country wrote to me about 12 of their patients, several of whom suffered from late neurosyphilis. One patient had died and two others were in a mental hospital Two were cases of Clutton's joints which were thought to be instances of Still's disease and in the third case a mother and two insufficiently treated children were lost to a follow up since the mother refused to accept the V15 transfer forms for a clinic in another part of the country into which she was moving

It is true that all 12 cases included in these three incidents concern older children and young adults, but they serve to show that the infantile symptoms were so masked as to be practically if not quite, unrecognizable or that, if they were diagnosed as congenital syphilis, the patients were so inadequately treated that *syphilis congenita tarda* including the maleficent neurosyphilis was able to occur in several of them. Hence the need for keeping the memory alert for the symptoms of the disease and for maintaining a moderately high index of suspicion for at least the next 25 years.

Diagnosis of congenital syphilis in infants

For the benefit of practitioners who may be located in areas where infantile congenital syphilis still has to be considered when making a diagnosis, the salient points to be remembered will be briefly recapitulated since they have already been more fully given in the individual sections of the chapters on symptomatology

A history of syphilis in the parents is rarely obtained, for frequently the mother is a Colles mother who has never had any signs or symptoms of the disease. One or more abortions or stillbirths are not so suggestive of syphilis to-day as they were before Rh incompatibility was discovered. We now know that erythroblastosis foetalis has to be considered in diagnosis so that the finding of the treponema of syphilis in scrapings of lesions or in sections of organs and tissues is of great diagnostic value. It is important to remember that all rashes, even in the napkin area, are not necessarily syphilitic beware of Jacquet's erythema (see Fig 28) Several patients with napkin rashes sent into my congenital-syphilis unit as cases of congenital syphilis were not syphilitic and proved to be examples of ammoniacal dermatitis. Snuffles from rhinitis may occur in non syphilitic as well as in syphilitic infants. To be diagnostic two or more of the symptoms or signs of the disease should be present. Parrot's pseudo-paralysis is an important manifestation but it is diminishing in incidence it usually occurs under 3 months of age and rarely after 4 months On the other hand, the paralysis associated with scurvy is rare before the sixth month and reaches its peak in the eighth or ninth month of life. Other causes of paralysis in infants especially birth injuries and Erb's paralysis were in the past not infrequently found to be associated

with or actually due to congenital syphilis, as was demonstrated by laboratory tests and radiological examinations. The diagnostic pitfalls inherent in these tests and examinations have been pointed out under their respective headings, the most important being (1) the unreliability of the W.R. under the age of 3 months (p. 81), (2) the value of a series of quantitative Wassermann tests in the first few months of life (p. 81), and (3) the recognition of the fact that various other infantile conditions and diseases may simulate many of the radiological appearances which were formerly considered to be diagnostic of congenital syphilis (p. 202). Saw tooth metaphyses and cat bite lesions of the tibia are now regarded as being the only X ray signs diagnostic of congenital syphilis. Hepatosplenomegaly in infancy is very suggestive of congenital syphilis, so are peeling hands and feet and a certain shininess of the skin of the extremities. Malnutrition or failure to thrive may be the only symptom of an otherwise latent syphilis. Observations on the diagnosis of congenital syphilis during the first few months of life are given in papers by Ingraham (1935, 1941), Christie (1938, 1939), Black (1939), Evans (1940) and Wenger (1945).

Diagnosis of congenital syphilis in older children

It has already been pointed out that the incidence of infantile congenital syphilis has been greatly reduced in this country, in the U.S.A., in Scandinavia and several other countries. The position with regard to late congenital syphilis is very different, certainly in this country and, according to Bauer (1949), also in the U.S.A. Too many patients are allowed to pass through the stage of infantile syphilis unrecognized, either through insufficient screening and treatment of infected mothers or through inefficient diagnosis and treatment of the infantile disease for the reasons given above. The responsibility for this rests largely upon the clinicians, particularly paediatric clinicians, medical and surgical. Too many patients are diagnosed as suffering from tubercle (of glands, joints, fingers, etc.) from rheumatism (of joints), from trauma (of bones, joints), from various nerve affections (such as meningitis, hemiplegia, paraplegia, unequal fixed pupils, encephalitis) or from mental deficiency and disorders of behaviour and intellect, whose pathological condition is really due to syphilis.

Patients with haemoglobinuria were, in our experience, frequently admitted to surgical wards, and examined and treated on surgical lines, in default of a simple urine examination for the presence or absence of red blood corpuscles. It is imperative, if congenital syphilis is to be eradicated in the foreseeable future, that in any of these conditions syphilis should be actively sought by taking a good personal and family history, by a thorough and searching clinical examination, by serological blood tests and by an examination of the cerebrospinal fluid in every nerve case and whenever the blood W. R. is positive.

Lastly on the discovery of a case of syphilis in a family be it a parent with general paralysis, tabes dorsalis, aneurysm or cardiovascular disease *or a child with congenital syphilis, steps should be taken to examine all* the other members of the family for latent or manifest syphilis and to treat at the earliest opportunity all those whose condition calls for treatment. This may need much patience and tact, but it is well worth doing and doing well.

Prognosis

The prognosis in congenital syphilis depends upon several factors, the most important of which is the age at which symptoms appear. All observers agree that the mortality was highest in infancy and the mortality rate before the modern methods of prophylaxis and treatment with penicillin were employed was between 40 and 70 per cent in different series of cases. Another important factor in prognosis was the presence of neurosyphilis especially clinical neurosyphilis in patients 1 year and over. This is shown by Table 18 (p. 283) where the over all mortality of patients aged 1 year and over was shown to be 6 per cent, whilst that of the non neurological cases was 1 per cent and of the patients with clinical neurosyphilis 35 per cent.

(*A*) *Prognosis in infancy*. In the absence of antisyphilitic treatment during pregnancy *primary or secondary* syphilis in a mother nearly always forebodes a serious outlook for the infant from the severity of the infection. Breast fed infants stand a better chance of survival than do the artificially fed and legitimate children than do the natural born. It has previously been stated that haemorrhagic patients and infants born with symptoms of the disease upon them almost always died though in my experience such cases were infrequent, and to-day they are distinctly rare in more enlightened communities. Among unenlightened peoples severe cases doubtless still occur and may take a heavy toll of the infant population. Other causes of infant mortality in our patients were (1) troubles with the taking of food on account of the difficulty in breathing through the nose (2) persistent vomiting and pylorospasm, possibly associated with the ulceration of the stomach and intestines which may be present in these cases (3) lack of assimilation of food particularly in artificially fed infants which may result in malnutrition and (4) the lability of syphilitic infants to various infections. Mortality was due to gastro-intestinal infections leading to vomiting diarrhoea, marasmus and dehydration to oral infections spreading down to the trachea larynx and lungs giving rise to laryngitis and sometimes a fatal bronchopneumonia, also upwards to the ear resulting in otitis media.

(*B*) *Prognosis in older children*. The prognosis in older children is much better than it is in infants and apart from neurosyphilis which was, and probably still is, a not infrequent cause of death in congenital syphili

tics, prognosis is possibly as good as in normal children (see Table 13 p. 273). The poorer physical and mental development which formerly was an accompaniment of congenital syphilis and is occasionally seen to-day may be due to the syphilitic taint in the parent and/or in the child If in the latter it may have been associated with an actual infection with the treponema, in which case a positive W R would be expected in infancy or the syphilitic taint in the parent may have weakened or adversely affected the germ plasm of the offspring in which case the W R. would be negative. On the other hand, the inferior mental and physical development of the congenitally-syphilitic individual formerly stressed may have been due to poorness of stock. We have no means of telling

Neurosyphilis is undoubtedly the most serious manifestation of late congenital syphilis, for we frequently found it possible to render the condition presumably inactive, the patient ultimately showing a negative blood W R. and a normal C.S F yet the scars of irreparable nerve damage persisted. Such were optic atrophy or other eye lesions old pars or hemiplegias, nerve deafness, cerebral scars giving rise to fits (usually called epileptic or epileptiform), progressive physical and mental enfeeblement culminating in the complete amentia of chronic G P I In addition to 28 deaths from syphilis in our patients over 1 year old of which we had records (26 per cent) there was an unspecified number of other patients who defaulted, often with a positive blood and spinal fluid, who without doubt have since died in institutions. In fact, I considered in the past that manifest neurosyphilis in older children was of bad prognostic import unless treatment were undertaken early and given intensively and its effect controlled by repeated C S F tests every 3 to 6 months and by clinical assessment. Even so the outlook was by no means encouraging Penicillin therapy has rendered the prognosis less gloomy

Criteria of cure

There were two criteria of cure (1) a permanent reversal of serological reaction in the blood and cerebrospinal fluid, and (2) permanent absence of signs of active disease In many cases of late congenital syphilis the W R. is very resistant and, as has been mentioned in Chapter 5 p 83 after having become negative following several years treatment, the reaction may be unstable and relapse again after a variable interval. It has been mentioned that in 10 cases we found the C S F relapsed in protein and cell content and in its W R. As regards the second criterion of cure—permanent absence of signs of activity—this certainly seems to occur in many of the cases, and such cases would be regarded as cured by most authorities. Personally I am not so sanguine for it is possible in my view for these patients to develop interstitial keratitis congenital G P I or tabes, and even arteriosclerosis, heart disease and aortitis in the fourth or fifth decade, possibly even with a negative W R A careful personal and

family history in a case of this kind might give a clue to the aetiology. Warthin it will be recalled said a syphilitic patient is never cured, and McDonagh said the same about congenital syphilis. From the point of view of the patient's psychological outlook it is probably wiser to be optimistic, yet to bear in mind the possibility suggested above of a congenital origin in any case in which the patient denies all possibility of venereal infection. In such event it might be necessary to consider the possibility of *acquired* syphilis in infancy or early childhood (Chapter 13).

'Spontaneous recovery'

Jeans and Cooke state in their book that they have seen 12 instances of apparent spontaneous recovery in children first seen during early infancy and 20 others in children first diagnosed after 2 years of age. Our own experience has not enabled us to register similar observations, for once congenital syphilis was diagnosed the patient was always treated. Occasionally a patient has been apparently cured by mercury alone or by one course of neoarsphenamine or bisoxyl, and only very rarely were we content to let the patient run the risk of too little treatment. Nevertheless we have seen cases of a mild infection in which the syphilitic symptom cleared up and the W.R. became negative and remained negative after a very small amount of treatment. Such recoveries, whether they be 'spontaneous' or after a minimal amount of treatment may be due to the normal mechanism of defence. In any event it is, we think, optimistic to talk of recovery in such cases in view of the possibilities mentioned under the previous heading. Aortitis, aneurysm, G.P.I. should these supervene later might be called acquired when they were really due to congenital syphilis.

Actually we have been able to keep in touch with only a few of our young patients. Usually as they grew older they were curious to know why they were brought to see us once a year for a blood test. The mother hardly ever told the child the truth and we felt that it was not our place or duty to perform what was the mother's duty, painful though it might be. Occasionally and usually after a talk on the wireless about 'inherited' disease, a former patient has written to us to ask about the treatment we gave her when she was a child. We have then usually told her about it, but as she had probably been well treated in childhood she has usually not needed further treatment. When however the inquiry about a former patient has come from a practitioner we have sent him a record of the patient's symptoms, treatment, and results of the blood and spinal fluid investigations, and if asked to do so, have made suggestions as to further treatment. *It is possibly due to the war years and the* scattering of London's population during the bombardment but we have been disappointed at not being able to remain in touch with more of our

former patients. Syphilis is such a chronic disease that it is not possible for one individual doctor to see a case of congenital syphilis through to the end—even with an ideal follow up system. We need to emulate the example of Alfred and Edmond Fournier where Edmond continued to remain in touch with and to supervise his father's patients after his father's death.

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CHAPTER 12

THE TREATMENT OF CONGENITAL SYPHILIS

1 Prophylaxis

THE ideal method of treating congenital syphilis is undoubtedly to prevent it, and it has on several occasions throughout the pages of this book been emphasized how important it is that every expectant mother should have a blood test as early as possible in pregnancy and be appropriately treated should she be found to have a positive W R. This was in the first instance all that was considered necessary but subsequent experience has shown that a woman may become infected later in her pregnancy and it is therefore desirable to repeat the test at the sixth or seventh month if the first test has proved negative. Formerly until the advent of penicillin, the arsphenamines were the drugs of choice for the prophylactic treatment of the mother but since the discovery of penicillin many investigators have shown that the drug can apparently be relied upon to prevent congenital syphilis in a large percentage of the cases in which it has been used alone. The infants born to the mothers so treated have been examined clinically serologically and radiologically in infancy and have been followed for several years with gratifying results

Recent observations of Mary Goodwin seem to point to the conclusion that a woman need not be retreated in any subsequent pregnancy if (1) she had previously been given 4 G or more of arsphenamine or its equivalent plus bismuth therapy or at least 2 4 million units of aqueous penicillin (2) she has no clinical signs of active infection and (3) she has a negative or only a low titre W R. These recommendations are stated by Goodwin to be valid irrespective of the stage and duration of the mother's infection at the time of her original diagnosis and treatment, and regardless of the interval which has elapsed between the previous treatment and the present pregnancy Personally I am of the opinion that a longer interval at least 10 years, should be allowed to elapse with careful follow up before Goodwin's conclusions can be regarded as justified

In this country we have hesitated to rely exclusively on penicillin for the prevention of congenital syphilis, and although it is being used here for that purpose it has practically always been used in conjunction with arsenicals or bismuth

2. Treatment

(A) Retrospect and prospect

The drugs in common use until recently were mercury and its various salts, the different arsenicals, bismuth and its salts and the iodides. Since the advent of penicillin the treatment of congenital syphilis has been entirely revolutionized, particularly in the U.S.A. and with the newer antibiotics we have perhaps reached an era when the treatment of syphilis like that of so many diseases, may advance by leaps and bounds though we must not lose sight of the fact that syphilis in man is such a protracted disease (or was so in the past) that we must wait for 10 and possibly more years before we can be certain that a cure has been effected. True, the effect of drugs can be tried on experimental syphilis in animals, but it is *not always safe to assume that a drug which is potent in rabbit syphilis* would have an equally beneficial effect in the human disease.

It appears that both the incidence and the severity of congenital syphilis are diminishing and the change has been taking place during the course of my own experience. It is quite uncommon to see a florid case of the disease in this country to-day which we owe mainly to two causes (1) the earlier and better treatment of primary and secondary syphilis in the parents, and (2) the diagnosis and treatment of the expectant mother. This however has had the effect of taking us off our guard, for although early congenital syphilis has greatly diminished, the later forms have not diminished to anything like the same extent. It is being taught to-day that infantile syphilis is a very rare disease with the result that students and practitioners of medicine and even paediatricians often fail to think of it when making a diagnosis.

Treatment with mercury is now largely of historical interest, but until as late as the second decade of this century the element itself or one of its salts (calomel perchloride, protoiodide) was extensively used in the treatment of congenital syphilis, often alone but also in conjunction with the arsphenamines. The drug is, or should be, so little relied upon nowadays that no further details will be given, but the reader is referred to the author's account in Garrod, Batten and Thursfield's Diseases of Children for details (4th edn. p 910 1949).

Potassium iodide held an important position in the treatment of acquired, especially tertiary syphilis and of congenital syphilis, particularly where bone lesions or gummata were thought to be present. Intravenous injections of sodium iodide have been recommended for juvenile tabes dorsalis. We tried it in 2 cases of early tabes dorsalis, starting with 10 ml. of a 10 per cent solution in distilled water and increasing by 2.5 ml. daily until a maximum daily dose of 5 G. was reached by the seventeenth day. In the case of the boy whose neurosyphilis was less severe than was the girl's

the W R. in the C.S F improved from 4.4. to 0 0 in 4½ years and the blood W R. became negative in less than 4 years. He certainly appeared to derive benefit from the iodide treatment. In the girl there were fits and the C.S F investigation pointed to the supervention of psychic manifestations and taboparesis. The blood and C.S F W R remained positive in her case although she was given much treatment including malaria, bistovol and arsphenamines in addition to the sodium iodide.

Then the *arsphenamines* were introduced and shortly after they had been used on adults their effect on children suffering from congenital syphilis was tested. Infants and small children, in whom intravenous injections might be difficult, were given neo-arsphenamine by the deep subcutaneous or intramuscular route.

When *sulpharsphenamines* were introduced, about the year 1919, they were used for deep subcutaneous and intramuscular injections and found much favour among syphilologists who had children among their patients. When the patients complained of the pain or inconvenience of the buttock injections, intravenous injections of neo-arsphenamines were substituted.

The preparation *mapharsen* (*mapharside*) is interesting because it is assumed to be the active derivative of neo-arsphenamine which is formed in the body when the latter is injected. The dosage of mapharside is about one-eighth that of neo-arsphenamine, and it has been used for the intensive treatment of primary and secondary syphilis, also for expectant mothers and in congenital syphilis. American and Canadian workers who have reported upon its use in congenital syphilis gave 6 weekly injections of the drug alternately with 6 weekly injections of bismuth or 6 weeks mercury treatment, without any rest periods. Anwyl Davies has used mapharside extensively since 1929 and now uses it exclusively as the arsenical drug of the trivalent type.

Acetarsol (*Acetarsone Stovarsol Orarsan Spirocid* etc.) has been in use since 1922 first as an oral *prophylactic* against syphilis and then for the oral *treatment* of the disease including congenital syphilis. The arsenic in acetarsol is pentavalent, as is also the case in acetylarsan and tryparsamide the latter has been extensively used in neurosyphilis, both by intravenous and deep subcutaneous or intramuscular injection.

In 1921 *bismuth* began to be used for the treatment of human syphilis and was found to be more efficacious and less toxic than mercury Shortly after its introduction it was associated with arsphenamines in the treatment of syphilis. Combinations of arsphenamine and bismuth compounds Bistovol (Levaditi) Bismarsen (Raiziss, 1925) and others have been prepared but they have not enjoyed a great vogue in this country

Finally we come to *penicillin* which was first used by Mahoney and his associates in 1943 for the treatment of early syphilis, and shortly afterwards for the treatment of syphilitic pregnant women (prophylaxis of congenital syphilis), and for the treatment of antenatal (congenital) syphilis (Ingra

ham, Mahoney Moore, Platou and others) from 1944 onwards. More recently still penicillin treatment has been combined with mapharside for the treatment of experimental syphilis in rabbits (Eagle and associates 1946 Selbie 1946) and in the same year Levaditi and Vaisman showed that a similar synergistic action between penicillin and bismuth operated in the case of experimental and clinical syphilis. The three drugs penicillin, arsenoxide and bismuth being synergistic in their action and not merely additive, it may well be, as was forecast by Eagle and his co-workers in 1946 that the best treatment of human syphilis will prove to be these three drugs in combination.

(B) Penicillin

When penicillin was found to be capable of killing the spirochaetes and clearing the lesions of experimental syphilis in animals and the acquired disease in man, its effect in congenital syphilis was thereafter soon tested at various clinics in the U S.A. The short term results were gratifying but some relapses, both clinical and serological were reported Various treatment schedules have been suggested, but with penicillin treatment in its present fluid state, any definite line of treatment suggested will doubtless be out of date by the time this book is published.

Goodwin (1950) writes The recommended schedule employing aqueous penicillin is a total dose of 100 000 units per kilo of body weight, given in 120 injections at 3 hour intervals for 15 days. Febrile reactions of from 1 to 3 F during the first 1–2 days of treatment occur in about half the patients, but they are not serious and soon subside, so that it is not necessary as a rule either to diminish the size of the earlier doses or to interrupt the treatment. The deaths which have occurred during penicillin therapy have been attributed to the severity of the disease itself or to complications, and not to the toxic action of the drug Consequently it is usually held that there is no necessity to start with schedules of gradually increasing doses. I cannot help feeling, however that it would have been risky to start with full-sized initial doses of penicillin on some of the very heavily infected babies we had to treat during and for some years after the first world war They succumbed after 1 or 2 small injections of sulpharsphenamine (0·02 G), and would probably have done better on a fortnight's treatment with mercury ointment or 1 or 2 small injections of bismuth oxychloride (0·005 G = 0·5 ml. bisoxyl) They might equally well have succumbed to ordinary starting doses of penicillin

Oral administration Henderson and McAdam (1946) gave penicillin to infants by mouth, and after 100 000 units had been thus administered, adequate concentration of the drug was present in the blood 12 hours later More recently Rose and co-workers (1949) have given calcium penicillin to infants by mouth in the form of tablets each containing 12 500 units,

the total amount given being $1\frac{1}{2}$ to $2\frac{1}{2}$ million units Four of the 5 patients, all infants, responded satisfactorily to this treatment, both clinically and serologically but the fifth patient, a child of $2\frac{1}{2}$ responded well clinically though his W R. remained positive even after retreatment.

Little has been written upon the use of *penicillin in older congenital syphilitics* an important paper dealing with this subject was published by Hanchett and Maude Perry in 1950 The patients forming the subject of their inquiry ranged in age from 6 months to 31 years, about half of them being under 2 years of age when they were first brought for treatment. The total dosage of the drug averaged 300 000 units per kilo/body weight for children under 2 150 000 units between the ages of 2 and 4, and 115 000 units per kilo for those over 4 years of age. The authors found that graduation of the earlier doses gave rise to only a very slight diminution in the reactions produced. An important observation was that 95 per cent of the reactions to treatment occurred in children under 2 years. *These reactions were febrile in character temperatures ranging between* 100 and 104 F were of short duration and in no case prevented completion of treatment. One patient with juvenile paresis, aged 19 years, showed a marked exacerbation of mental symptoms after treatment was started, and subsequently needed confinement in a mental hospital Unfortunately the later history of this patient is not recorded.

The conclusions Hanchett and Perry were able to draw were (1) that their evidence supported the results obtained by other workers that penicillin treatment is effective in congenital syphilis both in regard to therapeutic results and safety (2) that we shall have to wait for years of careful follow up examinations of treated cases before any conclusions can be *drawn as to the effectiveness of penicillin in preventing late manifestations* of the disease (3) that infants and children may be given total dosages of 300 000 units or even more per kilo body weight with little danger of reaction (4) in children over 2 it is the exception rather than the rule for the W R. to become negative and (5) if a negative W R. is to be obtained through penicillin treatment therapy should be given at the latest before the age of 2 years and preferably during the first 6 months of life

These observations tend to support earlier ones for example those of Yampolsky and Heyman who were not impressed by the results of penicillin treatment in cases of interstitial keratitis and Clutton's joints either clinically or serologically *It may well be that a combination of* penicillin with arsenic and bismuth may ultimately prove to be the best treatment for congenital as well as for acquired syphilis but the best combinations will have to be worked out on the lines of the clinical studies envisaged by Eagle Magnuson and Fleischman (1946). Substituting procaine penicillin for the aqueous solution I would suggest the following outlines of treatment for patients of increasing body weight

For infants up to 5 kilos body-weight

Procaine penicillin 100,000 units daily (for 15 days)
Mapharside (mapharsen) 1 mg twice weekly or Monday and Friday given intravenously at elbow or in external jugular vein or by intramuscular or deep subcutaneous method.
Bismuth oxychloride (bisoxyl) 0·05 ml. twice weekly on Wednesday and Saturday by intramuscular or deep subcutaneous method.

The above schedule is for 15 days. Afterward continue mapharside 1 mg per kilo/body weight on Wednesdays, alternating with bisoxyl 0·1 ml per kilo/body weight on Saturdays, each week for 8 to 10 weeks.

For children from 5 to 10 kilos body-weight

Procaine penicillin 100 000 units daily (for 15 days).
Mapharside 2 mg twice weekly on Monday and Friday given as recommended above.
Bismuth oxychloride 0·1 ml. twice weekly given as mentioned above.

This schedule is for 15 days. Thereafter continue mapharside 1 mg per kilo/body weight on Wednesdays, alternating with bisoxyl 0·1 ml. per kilo/body weight on Saturdays each week for 8 to 10 weeks.

For older children from 10 to 20 or more kilos body weight

Procaine penicillin 200 000 units daily (for 15 days).
Mapharside 4 mg twice weekly as recommended above.
Bisoxyl 0·2 ml twice weekly as recommended above

This schedule is for 15 days. Thereafter continue mapharside 1 mg per kilo/body weight up to a maximum dose of 10 mg (0·01 G) on Wednesdays alternating with bisoxyl 0·1 ml. per kilo/body weight up to a maximum of 1 ml. on Saturdays each week for 8–10 weeks.

The blood W R. and the C S F (if possible) should be tested before the treatment is started. The S W R. should be tested again after 1 2 3 and 6 months, quantitatively if possible. Should the W R. be almost or quite negative and there is no clinical relapse, no further treatment need be given, but the S W R should be tested again at 9 and 12 months and thereafter at 6-monthly intervals during the ensuing 2 years, and yearly afterwards. If the W R. is still definitely positive after the *first* 6 months, or if the W R. having become negative later relapses, the course of treatment should be repeated adopting the schedule according to the body weight of the child. In the event of the C S F showing evidence of neurosyphilis the treatment indicated in Chapter 8 p 323 should be carried out (with the addition of penicillin).

Much information on the prophylaxis and treatment of congenital syphilis and many allied subjects will be found in the Transactions of the International Symposium on the Study of Syphilis held in Helsinki in September 1950

(C) Arsenic

The original arsphenamine ("606") is nowadays not used at all in this country and was formerly only rarely used here for the treatment of congenital syphilis. Many brands of neo-arsphenamine were tried since our clinic started in 1917 but those most frequently used were Novarsenobillon (N.A.B.) and Bayer's 914. These have to be dissolved at the time of use in sterile doubly-distilled water. The diglucoside of arsphenamine (Stabilarsan, Boots) is supplied in ampoules in liquid form ready for injection. When sulpharsphenamines ("Sulfarsenol" and allied drugs) were introduced they were extensively used for deep subcutaneous and intramuscular injection in our patients. All the aforementioned drugs, as well as mapharsen which we did not use in our clinic, contain the arsenic in trivalent form. Of the pentavalent arsenicals we used tryparsamide for congenital neurosyphilis and acetarsone ("Stovarsol") for the oral treatment of congenital syphilis fairly extensively, but we have no personal experience of the use of acetylarsan injections, the diethylamine compound of acetarsol.

Dosage of arsenical drugs. Infants and children tolerate arsenic preparations quite well, even more so than do adults. They can take 30 mg (0·03 G.) per kilo body weight, which represents about 0·1 G. of neo-arsphenamine for an infant of 3 to 4 kilos. It was not our custom to give quite such big doses, though it seems to have been customary in Germany (Müller 1927).

For a first course we injected 20, 40, 60, 80 mg., 0·1 G. (twice) and 0·12 G. (twice) of neo- or sulpharsphenamine, totalling 0·64 G. in 8 doses. Mercury in the form of proto-iodide gr. ⅛ (8 mg.), two or three times a day was associated with the arsphenamine injections. After a rest of 4 weeks the W. R. was tested and a fresh course of treatment begun. This was started at 60 mg. and increased to 0·18 or 0·24 G. for the seventh and eighth doses; the mercury iodide was slightly increased—to ¼ gr. (16 mg.) twice a day. After another month's rest the W. R. was again tested. It was found that the W. R. varied considerably in the time taken to become permanently negative, and that several factors seemed to play a part: (1) the age of the child when treatment was started, (2) the presence or absence of neurosyphilis in the patient, hence the importance of examining the C.S.F. at the commencement of treatment, (3) the age of the infection in the parents, particularly the father, and (4) whether or not the patient received treatment regularly. A patient whose C.S.F. had been found positive would have the fluid examined every 3 months until it was quite negative, and after a negative blood and fluid had been obtained, we were usually content to give one extra course of treatment, though this one extra course was later increased to two. As the patient increased in age and size, so naturally the doses of the drugs given would be

increased until a maximum of 0·45 G of neo- or sulpharsphenamine was reached about the age of 8 to 10 years. The mercury iodide would also be increased, possibly to gr ½ (30 mg) once or twice a day and probably by this time the injections would no longer be of sulpharsphenamine intramuscularly or deep subcutaneously but of neo-arsphenamine intravenously. Intravenous injections are possibly more convenient to give to bigger children and better tolerated by them but they are not so satisfactory as intramuscular injections, since the drug is more rapidly eliminated after intravenous injection. We therefore preferred to carry on with the deep subcutaneous or intramuscular injections as long as the patient could conveniently tolerate them. For the latter the dose should be 1 ml. and not more than 2 ml. and for intravenous injections 3 to 5 ml. should suffice. Arsphenamine diglucoside (Stabilarsan) which is supplied dissolved ready for use, must be injected very slowly to avoid the possibility of unpleasant after-effects. (A good plan is to aspirate some blood into the syringe three or four times during the injection of the drug and to reinject the mixture.) Mapharside being a more potent drug than neo-arsphenamine, 7 or 8 times as potent is given in correspondingly smaller doses. For practical purposes

	60 mg or 0·06 G	mapharside is the equivalent of			0·45 G	neo-arsphenamine
	40 mg or 0·04 G	"	"	"	0·3 G	"
and	20 mg or 0·02 G	"	"	"	0·15 G	"

The technique of these injections can best be learnt by practical demonstration and experience in a clinic. (Harrison's monograph in the Encyclopaedia of Medical Practice may also be consulted with advantage.) There are two points which experience has taught us should be emphasized

1 All intravenous injections should be given with great care so that none of the drug escapes into the perivascular tissues, otherwise a painful swelling will ensue, leading possibly to necrosis. This would not be very conducive to the patients regular subsequent attendance for treatment. To prevent this happening once the point of the needle has entered the vein and the drug seems to be going in well, keep the eye fixed on the vein and at the first appearance of a swelling on or along the vein *stop injecting the drug* and withdraw the needle a short distance, for it may have gone forward and pierced the deep wall of the vein. Withdraw the piston a little and if blood now flows into the syringe it is probably safe to go ahead slowly with the injection. If swelling around the vein recurs or continues, the attempt should be abandoned in that arm and the other arm tried.

2. For gluteal injections in children the patients are best lying prone with both legs relaxed and the toes turned in of the leg to be injected. A point is selected about midway between the anterior superior iliac spine and the upper end of the cleft between the buttocks, and an antiseptic applied. A sterile needle, about 1¼ in. or 3 cm long is thrust into the muscles at the point indicated and at right angles to the surface of the body After waiting for a few seconds to see that no blood oozes from the needle, the latter is held by the base and the syringe, charged with the drug to be injected is fitted to it and the injection slowly given. No pain running down the leg should be felt by the patient if

there should be pain the needle must be withdrawn and reinserted elsewhere. The injection having been successfully given, the syringe and needle are withdrawn and the buttock well massaged with gloved hand enclosing a wad of gauze or cotton wool. When giving a deep subcutaneous injection, which is also done in the upper and outer quadrant of the buttock region, care must be taken, by drawing away the skin and subcutaneous tissues from the overlying muscle, that the needle point is movable over the fascia and not too superficial. One has seen several very sore buttocks from injections of arsphenamine, bismuth or tryparsamide given too superficially.

A course of arsphenamines consisted usually of 8 weekly injections and some of our patients were given as many as 60 or 70 injections totalling 30 G. of neo- or sulpharsphenamine over a period of 4 years before they were regarded as "cured." Tryparsamide, which was substituted for the trivalent arsphenamines when neurosyphilis failed to respond adequately to the latter drugs, was given by intramuscular, deep subcutaneous or intravenous injection. The usual dose for a child of 1 or 2 years is 0·5 to 1 G. dissolved in 1 ml. of distilled water and injected weekly for 12 weeks. The dose is increased proportionately to the age, so that a child of 12 may be given 2 G. or even 2·5 G. for a dose. As stated on p. 324, tryparsamide was frequently given mixed with bisoxyl for the usual 10 or 12 weekly injections. Tryparsamide has an effect upon the optic nerves, so that the fundi should always be examined by an ophthalmic specialist in order to obtain an opinion as to the advisability of using the drug in a particular patient. I did not come across a case in which tryparsamide treatment of a child had to be suspended because of any visual trouble.

Acetarsol (Stovarsol). With the advent of penicillin and its wide use in the treatment of infantile congenital syphilis, either alone or in association with injections of mapharsen and or bismuth, it is unlikely that the oral treatment with acetarsol will ever be reintroduced and the reader is referred to the author's experiences with this drug which were recorded in 1941.

Toxic reactions to trivalent arsenicals

Infants and children tolerate arsphenamine treatment well, even better than do adults, probably because their excretory organs, especially the liver and kidneys, are in a healthier condition. Reactions may occur, however, and they may arise at varying periods after the injections have been given.

(1) Immediately or within a few minutes.
(2) After a few hours up to 24 hours.
(3) Late—after 1 to 5 days.
(4) Remote or cumulative effects, that is, towards the end of a course or courses of treatment.

In addition to the above there are the Jarisch Herxheimer reactions which are due to an increase of syphilitic signs or symptoms, and which may be serious if they affect vital organs, such as the heart or brain

(1) **Immediate reactions** There seems to be no doubt that some of the reactions which occur such as a slow or a rapid pulse, a feeling of faintness or an actual faint, are not really due to the drug but to the mere prick of the needle they are doubtless psychic in origin and due to para sympathetic stimulation. Vomiting would come into the same category and we had one patient who vomited regularly every week before the in jection was given Vomiting sometimes occurs immediately after an injection, especially if contrary to instructions a heavy meal has been taken shortly before coming to the clinic. The commoner immediate manifestations are the vasomotor disturbances, often referred to as "anaphylactoid or nitritoid crises—congestion or swelling of the face neck or hands, a rapid pulse, dilated pupils, a sense of constriction about the throat and praecordial distress, which are thought to be due to damage to the capillary endothelium. These symptoms might be due to an immediate Jarisch Herxheimer (toxic) effect upon the capillary endothelium, which soon passes off without doing any permanent damage. In several of our early patients the doses we injected were too big for example, 0·45 G in children of 5 or 6 years. One boy to whom we gave such a dose was brought back to the clinic within a few minutes with swol len hands, cyanosed and vomiting Another patient was ill for 2 weeks with fever diarrhoea and sickness after a dose of 0 45 G

We had 3 families in which 2 members shared the sensitivity to arsenic. A girl of 11 developed a generalized urticaria about 10 minutes after an injection, so it was thought wise to use Ametox (sodium thiosulphate) as the diluent for the arsphenamine, which was the treatment in those days The girl s mother was equally susceptible to arsenic, we were informed later A boy aged $2^{8}/_{12}$ years developed an immediate generalized ery thema after only 0·1 G neo-arsphenamine, but he was subsequently able to tolerate six 9-week courses of acetarsol (Stovarsol) After he had passed out of my care he was given a course of sulpharsphenamine when he was 5 years old After the first 2 injections, which were followed by pallor a poor pulse and vomiting the medical attendant, viewing these reactions as psychic and not toxic, proceeded with and finished the course of treatment (1940) The boy s mother was also susceptible to arsenic, for an injection of 0·45 G neo-arsphenamine gave her headaches and dizziness for a week. In addition we had a third family of which 2 members, a brother and sister were susceptible to arsenic.

Among other immediate symptoms of which our patients have com plained were tingling in the hands and feet in one case and a taste as of garlic in the other Both these patients were congenital mothers and the symptoms were not serious. A girl who was born during the first world

war and received little mercurial treatment in infancy was seen again at the age of 11 with latent syphilis and had a W R test on account of suggestive incisor teeth She was given 13 5 G arsphenamine diglucoside (Stabilarsan ') in 41 injections without untoward effect but with a persistent W R. and Kahn. After 26 bismuth injections the W.R. was less strong and it was hoped to complete the course with neo-arsphenamine, as bismuth had occasioned a stomatitis After each injection of Novarsenobillon (0 3 G) the patient was sick and had fits of sneezing and after a different brand of neo-arsphenamine (Bayer 914 ') the patient did not vomit but sneezed as before. This was the only patient we had who was thus affected

It is strange that in at least 2 patients symptoms occurred shortly after *subcutaneous* or *intramuscular* injections of sulpharsphenamine one was an infant who at the age of 6 months became cyanosed after an intra muscular injection of 0 12 G and was drowsy all the way home. The other was a girl of 2½ years who was sensitive to arsenic, for after the first injection of only 60 mg sulpharsphenamine small vesicles appeared on the arms and buttock on another occasion she shivered and went blue in the face after an injection and recovered in half an hour and on yet another occasion she was faint and felt ill half an hour after the injection. It is difficult to say whether such reactions were toxic or due to a Herxheimer or psychic reaction possibly they had a dual origin

(2) **Reactions from a few to 24 hours after injection.** That many of our patients had somehwat delayed reactions we attributed to the fact that they had to travel long distances by bus or train to reach their homes. Some of them were sick on the journey and the sickness thus started often continued for one or more days. Sometimes there was fever for a day or two occasionally headache and rarely a rigor The reactions mentioned under the headings (1) and (2) could be prevented or at least mitigated by strict attention to the technique of preparing the solutions (freshly, doubly-distilled water and not letting the solutions stand after being made) and by injecting them slowly Glucose (barley sugar) given to the children to suck while they were waiting for their injection appeared to have a beneficial effect Skin reactions—itching erythema or urticaria—are an indication to proceed with caution

(3) **Reactions after 1 to 5 days late reactions** (*a*) *Dermatoses.* The first 5 days after an injection seem to be critical ones If the patient has shown any evidence of skin sensitivity the erythema may become generalized and be diagnosed by an unwary outside practitioner as measles, German measles or scarlet fever We have seen such cases that were sent to a fever hospital only to be returned as being not an infectious fever on the other hand one of our patients who lived a considerable distance from the hospital was treated by his private doctor as a case of measles and when he returned to the hospital at the end of a week he was gravely

ill with exfoliative dermatitis and died shortly afterwards. He was 4½ years old, had received only 4 injections of neo-arsphenamine, totalling 0·75 G., and unfortunately was a case of latent syphilis who had been re-discovered after a long default since infancy. At the autopsy the pial vessels were injected and punctate haemorrhages were present in the cortex of the brain, so that the patient had both exfoliative dermatitis and haemorrhagic encephalitis after as little as 0·75 G. neo-arsphenamine.

Fortunately not all cases of arsenical dermatosis end as tragically as the one just narrated. As an instance we may mention the case of an infant of 3½ months. The clinical diagnosis based upon a rash, snuffles, enlarged spleen, typical facies with enlarged scalp veins and craniotabes was confirmed by the X-ray findings of typical osseous lesions of the femora, tibiae and ulna. The infant was treated with bismuth oxychloride, of which she received 22·6 ml. (=1·8 G. bismuth) in 23 injections, with monthly intervals between the courses. She was then nearly 10 months old and the blood and spinal fluid W.R. were negative. As albumen was present in the urine the bismuth treatment was suspended and neo-arsphenamine given. The child received 4 weekly injections 0·1, 0·2, 0·2 and 0·3 G.; she was only a year old and already had albuminuria from bismuth therapy, so it is not surprising that she developed an arsenical dermatitis with a rash on the trunk, arms and legs. Fortunately the injections were stopped and, after an exacerbation and spread on to the face during the succeeding week, the dermatitis gradually subsided, but with ebbs and flows and with the temperature raised to 102 and 103° F. Apart from local applications of olive oil and vaseline, the only internal treatment given was calcium gluconate 10 gr. (0·65 G.) t.d.s. by mouth. The infant eventually did quite well and at the age of 4 years the W.R. was still negative and the kidney function tests were all satisfactory. The sedimentation rate had fallen from 71 mm. to 8 mm. in the hour in 17 months. Unfortunately the war put an end to further observation of the patient.

A milder form of erythema than generalized exfoliative dermatitis is that described by Milian as "the ninth-day erythema" which is also generalized and accompanied by somewhat alarming constitutional symptoms, including pyrexia, often intense itching and possibly sickness and diarrhoea. Actually the condition may start on any day from the seventh to the eleventh after the beginning of the arsphenamine treatment and 1 or 2 days after an injection (Harrison). The condition is very uncommon and we did not encounter one case during the course of our 22 years' experience at Great Ormond Street.

During the second world war, however, we saw a patient of Dr. Waterfield who developed a severe dermatosis after neo-arsphenamine treatment which was diagnosed as a case of Milian's erythema. It concerned a girl of some 18 years, healthy and robust looking and a worker on the land

She was being examined as a blood donor and was found to give a positive W R. It later transpired that she was a latent congenital syphilitic and her mother developed general paralysis The girl was being treated with small doses (0·3 G) of neo-arsphenamine and had to bicycle several miles to and from the clinic in unusually hot weather and did not desist from her land work. As a result, and possibly in consequence of unusual action of the skin, after the third injection she developed marked pyrexia and an erythematous rash over the whole body For some days the girl was delirious and seemed gravely ill. Shortly afterwards she came under our observation and her condition was showing signs of improvement, so that she was diagnosed as suffering from the milder form (Milian's syndrome) of arsenical dermatosis. This was borne out by her later treatment, which was begun 2 months afterwards and consisted of 3 courses of 12 injections each of neo-arsphenamine (0·45 G) together with bisoxyl (1 ml. doses). The W R. remained persistently positive the C S F was quite negative. Dr Anwyl-Davies gave her 3 courses of mapharside and bismuth oxychloride without the patient having any reaction to the arsenic or bismuth. Finally she was given a course of 3 million units of penicillin in oil (300,000 units for 10 days) but unfortunately did not re attend for a further blood test.

For the treatment of severe dermatoses the latest drug to be tried is dimercaprol (B.A.L.—British Anti Lewisite) the dose for children being 1 mg per kilo body weight daily B.A.L. should not be given if the liver is likely to be already affected.

(*b*) *Severe cerebral symptoms* Fortunately severe cerebral symptoms were not common in children but we encountered at least half a dozen cases. The syndromes were of two different types 1 *Haemorrhagic encephalitis* leading to a rapidly fatal termination This is probably a true toxic effect of the arsenic. 2 *Acute focal lesions of the central nervous system* probably due to the occlusion of arteries which are the seat of syphilitic disease, the occlusion resulting from an overdosage with arsenic—a type of Jarisch Herxheimer reaction We saw instances of both types of lesion.

1 One case of ***haemorrhagic encephalitis*** which complicated a condition of exfoliative dermatitis has already been recorded (p 422) Our other case occurred as follows

A boy of 10 years with latent syphilis was the brother of a child who died of florid congenital syphilis. The boy's only stigma was typical Hutchinsonian teeth. He was given 4 weekly injections of neo-arsphenamine 0·2, 0·3 and 0·4 G (twice) with mercury iodide pills, gr ¼ (16 mg) bis die The last 2 doses were evidently too big for this particular patient. History does not relate what happened during the first 4 days after the last injection but on the morning of the fifth day the boy "had a fit, he went stiff and blue with spasms." A few hours later he was admitted to a hospital nearer to his home without our being apprised of the fact and the following details were obtained from the authorities

of that hospital. On admission the lad was semi-conscious and resented interference. Respiration was rapid the jaws were clenched and the Hutchinsonian teeth were noted. The neck was rigid and the arms and legs felt spastic. Bilateral Kernig's sign was present. The knee and ankle jerks were increased the plantar response was flexor Left pupil slightly larger than the right. T 100·8° F Pulse 128. Resp. 32 Few rhonchi were heard in the lungs Luminal gr 1½ was injected About 2 hours after admission lumbar puncture was performed under a general anaesthetic. Few ml of blood-stained fluid obtained, not under pressure many red and white cells were present. The patient died 12 hours after the fit he had in the morning" As already stated, our hospital was not informed of the patient's death and we had no opportunity of seeing the post mortem. The brain is described as being "swollen with flattened convolutions" and the cause of death—"encephalitis."

2. *Severe damage to the brain as a result of overdosage* We had two well-marked instances of this.

An infant who from the age of 3 months received 1·6 G neo-arsphenamine (3×0·1 2×0·2 and 3×0·3 G) and in addition solution of mercuric chloride, 1 in 1,000, 0·6 ml. for 2 weeks, 1·3 ml. for 1 week and 2 ml. for 2 weeks. When first seen by us at the age of 6 months the W R. was negative the head was asymmetrical and the child had a badly-united fracture of the left humerus. At the age of 8 months the infant developed screaming attacks, which persisted till death at 10½ months. Post mortem there was porencephaly (see Fig 84) following occlusion of a branch of the posterior cerebral artery

The second example of gross overdosage is exemplified by the following case

A child of 8 months after convulsions developed a hemiplegia which was diagnosed in India as polio-encephalitis. At the age of 2½ years she was seen by a London paediatrician, who thought the trouble had been polio-encephalitis but that she would get well and could return to India. *He did not examine the blood or cerebrospinal fluid.* Syphilis was first diagnosed at the age of 3⁴/₁₂ years, and retrospectively one would have no hesitation in stating that the patient had suffered not from polio-encephalitis but from congenital neurosyphilis. When the diagnosis was established the disease was treated but with such big doses (6 injections of neo-arsphenamine each of 0·5 G) that the results were disastrous. The child developed jaundice and paralysis of the limbs. The diagnosis now was epidemic jaundice and the child was sent to a fever hospital The fever hospital authorities having confirmed the blood and C.S.F with a positive W R. returned the child to the original hospital with the diagnosis of syphilitic myelitis. When we saw the child again later she appeared to be mentally defective. At the age of 8 years in 1941 the limbs were flail-like and the orthopaedic surgeon's prognosis a very gloomy one since then contact with the patient has been lost. My reading of this case was that the child had originally suffered from congenital neurosyphilis which was aggravated by overdosage with neo-arsphenamine

(4) **Remote or cumulative effects.** *Liver* Acute hepatitis leading to jaundice is (or was) a common complication of arsphenamine therapy in adult acquired syphilitics. It is now generally believed, however that in the majority of these cases it is not the arsenic that is responsible, but

that the condition results from a virus infection transmitted from patient to patient by an inadequately-sterilized syringe Anwyl Davies (1943) does not agree and came to the conclusion that the jaundice and dermatitis which so frequently followed the administration of arsphenamines were due to the toxicity of the different commercial brands of neo-arsphenamine, which varied from brand to brand of the different manufacturers and even from batch to batch of a brand made by the same firm. He attributed this toxicity to the variability in its manufacture which led to the variation of its arsenic content from 18 to 21 per cent, as well as to its various impurities. Furthermore, the toxicity of neo-arsphenamine is increased by oxidation so that solutions of this drug as also of sulph arsphenamines, should be *injected immediately they are prepared* Far less toxicity accompanies the use of arsenoxide, which Rosenthal (1932) confirmed is formed in the body after the injection of arsphenamines, and the preparation mapharsen (called mapharside in this country) is the one which Anwyl Davies used in his later investigations. As the result of his investigations he concluded that the more stable and purer drug mapharside produced far fewer cases of toxic jaundice and dermatitis than did the neo-arsphenamines, and he is of the opinion that there is little or no evidence that the injection of the drug activates the virus of hepatitis already present in the body (personal communication 1952)

It is generally agreed that jaundice complicating arsphenamine therapy is much less common in congenital than in adult acquired syphilis. There are various possible explanations. The child's liver may be less sensitive to the toxic effects of arsenic or to the virus of homologous serum jaundice Possibly also the fact that intramuscular injections are used for children in preference to intravenous therapy may reduce the chances of transmission of the virus We certainly had very few cases of jaundice among our patients and we like to attribute this to the care we bestowed on the sterilization of our syringes and on the preparation of the solutions for injection

Two of our patients at 8 years of age developed a true syphilitic hepatitis one (I P see p 171) became jaundiced during treatment with arsphenamines the other (A.B p 169) had various forms of treatment including arsphenamines, which benefited the liver condition without giving rise to jaundice Of our other patients who developed jaundice during treatment the majority were probably cases of *acquired* syphilis in fact, when a child developed jaundice during treatment we re-examined the history to see if by any chance the infection could have been an acquired rather than a congenital one The following cases illustrate this point

1 Cyril S. was a healthy infant and put out to nurse with a woman for a few hours each day while his mother went to work. It is possible that he might have been infected then but he showed no symptoms or signs of disease at the

time. At the age of 9 years he was found to be a diphtheria carrier and while in the fever hospital he developed a sloughing ulcerative condition of the tonsils and nasopharynx which suggested syphilis. This was confirmed by a blood test and the patient was then given antisyphilitic treatment, though it was very inadequate. He was brought to Great Ormond Street at the age of 10 when the diagnosis of syphilis was confirmed and the treatment with arsenicals and bismuth continued. His history was carefully investigated and he was found to be the only positive reactor in the family so it was quite likely that, as his mother had thought, the boy had contracted syphilis after birth and this surmise was strengthened by the fact that he suffered from jaundice as a result of the arsenical treatment (see p 424).

2. *In another case, that of a boy who was born in April 1915 and whose mother* and older sister had syphilis, the boy was perfectly well in infancy and child hood, and when seen at the age of 8 he had no symptoms but a positive W R. when examined routinely since his sister had severe neurosyphilis. During treatment he developed jaundice after he had received only 22 injections of arsphenamines totalling 6·45 G This, taken in conjunction with the fact that he had previously shown absolutely no symptoms of the disease, suggests that his syphilis may have been acquired either from his sister who was 2 years his senior or from his mother

Jaundice is recorded in 4 further cases in our series. In 1 of them it confirmed the diagnosis of acquired syphilis made on other grounds, and in at least 2 of the remaining 3 cases it is quite possible that the syphilis may have been acquired.

For the treatment of jaundice the further administration of the drug should be stopped and the patient kept in bed on a light diet. Stomachic sedatives may be given to counteract vomiting We gave our patients intravenous injections of sodium thiosulphate, 0·45 G in 10 ml. solution on alternate days. Harrison recommends giving intravenous injections of glucose, 10 to 20 ml. according to age, of a 30 per cent solution on the days between the injections of the thiosulphate.

Kidney Albuminuria is rarely occasioned by the arsphenamines in congenital syphilis, but we had one case of parenchymatous nephritis

A girl nearly 12 years old gave the following history At 9 years of age she developed Clutton's joints (knees) for which she was given no antisyphilitic treatment. A year later she had interstitial keratitis of the left eye, for which she was given neo-arsphenamine injections at an eye hospital. After having received 6·3 G of the drug, the patient had sudden abdominal pain, vomiting and diarrhoea. Two days later the abdomen became swollen and a week from the onset of the present trouble the patient was admitted to Dr Frew's ward in the Children's Hospital with "ascites and oedema of the legs. The urine was scanty contained a few red cells and was "solid with albumen. Blood urea was 41 mg % blood cholesterol 280 mg % (normal 100–200). There was slight shifting dullness due to ascites the laevulose test gave a normal curve the urine albumen was + + + The diagnosis was parenchymatous nephritis, which was almost certainly due to arsphenamine. As we had not previously encountered a case of arsphenamine nephritis we had not made it a rule to examine the patients urine before each injection of arsphenamine as we did with bismuth injections, but after this experience of 1932 we subsequently

examined the urine before all injections, but without finding serious albuminuria in another arsphenamine patient.

The patient did well, being kept in bed on a light diet the arsphenamine injections were of course stopped. Six weeks after admission the urinary output suddenly increased from 20 to 50 oz. (600–1500 ml.) in the 24 hours. The blood pressure was normal throughout, but some albumen was present in the urine during the 3 months the child was in hospital. She was then discharged to a convalescent hospital and later returned to the V D Clinic. After a year the W R. being still positive and the urine being free of albumen, arsphenamine treatment was resumed, but the patient had a reaction after each injection (rigor headache and sickness) and subsequently had a reaction (sickness and a headache in the evening of the injection day) even after an intramuscular injection. She was better but still had a weak W R. (3 1.0.0.) when she was lost sight of at the age of $14^{2}/_{12}$ years.

Toxic effects of the pentavalent arsenicals

Tryparsamide has in the past been very freely used in the treatment of neurosyphilis and it is surprising how much of the drug tolerant patients can take without harm. Harrison mentions that in adults amounts of 150 to 250 G of tryparsamide are quite common. Our largest doses in children have been around 60 to 65 G which were well tolerated. Two of our patients who had bigger doses, 79 and 116 G respectively complained of toxic manifestations one, a girl of 12 had flushing and sweating of the face 5 minutes after an injection and some of the other injections of tryparsamide with bisoxyl disagreed The other patient was a boy of 12 with whom the last 4 or 5 injections of tryparsamide (2 G intravenously) disagreed The mother complained that the boy went white on the way home and on one occasion he fainted and lost consciousness in the train with cramps in the stomach and shivering Another patient, a girl of 11½ years who suffered from tabes dorsalis, complained of sickness and headache after the later injections, 2 G each, of the first course of tryparsamide. We did not see any cases of arsenical dermatitis after the administration of tryparsamide

We saw several cases of skin rash after the oral administration of acetarsol (Stovarsol) usually rubelliform, sometimes scarlatiniform. On two occasions patients exhibiting such rashes were sent to a fever hospital by a resident doctor in my absence, only to be returned a few days later as being non infective. It is important to bear in mind the possibility of a toxic drug rash whenever arsenic is being administered. Several of our stovarsol patients had diarrhoea and vomiting sometimes associated with a rise of temperature to 100 or 101 F

General symptoms of saturation with arsenic or of overtreatment

Sometimes towards the end of a course of treatment and particularly after several courses of arsphenamine r other arsenical a patient may

exhibit indefinite symptoms of intolerance such as lassitude, loss of appetite and loss of weight. These are danger signals a warning that arsenic treatment should cease and an indication that a convalescence in the country or at the seaside for a month or longer if necessary should be recommended.

Jarisch-Herxheimer reactions

By a Jarisch Herxheimer reaction is meant an increase in the syphilitic signs or symptoms shortly after the institution of treatment. It is difficult to determine the nature of such reaction, whether it is a toxic effect of the drug itself or the effect of the dying or dead treponemata destroyed by the arsphenamine. Acting on the latter assumption, it was frequently recommended to start treatment with a milder drug, such as mercury or bismuth and even with penicillin as the drug of choice, some authorities consider it advisable to use graduated doses of the antibiotic for the first day or two of treatment. Caution is particularly desirable when the blood vessels of the heart or brain, or a delicate organ such as the eye, may be involved for here even a temporary occlusion may have serious effects upon the tissues supplied by these vessels.

Several types of the reaction have been described above. The early febrile and vascular disturbances may be Herxheimer reactions rather than due to the arsenic *per se* The most important Herxheimer reactions are those in which the blood vessels of the central nervous system become occluded, either by thrombosis or by swelling of the involved vascular wall following usually overdosage with arsenic. The two cases described above no doubt come into this category Reference has been made (p 109) to a rare type of the reaction we encountered.

A girl of 3 with a laryngeal stridor was operated on for what was thought to be a papilloma of the larynx. She relapsed after a temporary improvement and nearly died from suffocation After intubation masses were seen in the larynx on laryngoscopy The W R. having been found positive, the child was given 2 injections of neo-arsphenamine, when immediately after the second injection she had a sudden attack of dyspnoea, which was thought to be due to a Herxheimer reaction She died a few days later after an unsuccessful attempt at reintubation. Unfortunately no autopsy was permitted

(D) Bismuth

Since the introduction of bismuth therapy by Sazerac and Levaditi in 1921 the drug has been extensively employed in France, and soon after in many other countries, in the treatment of syphilis. It is more efficacious than mercury and, on the whole, less toxic our own experience with children bears out this view Owing to the generally favourable opinion of the value of bismuth, many preparations of the element have been placed upon the market and a list of those which have been used in this

country will be found in Harrison's monograph. They include (i) water soluble, (ii) oil-soluble, and (iii) insoluble preparations. In our clinic we used all three types of preparation, but soon gave up using the first two because they needed to be given 2 or 3 times a week on account of their rapid absorption and excretion. For many years we relied upon the insoluble preparations at first bismuth metal and afterwards bismuth oxychloride, which had been shown by Lomholt to have a fairly even and not too rapid absorption (1929).

Dosage and method of administration of bismuth. As the dose of bismuth for infants is rather a small one it is advisable to give the first few doses with a "tuberculin" syringe in which the millilitre is divided into twentieths. For an infant of 3–4 kilos 0·01 ml. of bisoxyl suspension[1] is recommended for a starting dose. This contains 10 mg. bismuth oxychloride or 8 mg. bismuth. It is usually safe to increase the dose by 0·1 ml. each week so that a maximum of 1 ml. is reached by the tenth injection, and if the infant appears to tolerate the injections well the eleventh and twelfth injections of the course may also be 1 ml. The urine should be tested before each injection for the presence of albuminuria and casts. If either of these be present in more than minimal amount or number the injection should be postponed for a week. It was our experience that it was not usually necessary to interrupt the first course of injections and that it was more likely to be necessary to do so in later courses. Lesions usually clear rapidly with bismuth treatment and we frequently found the W.R. negative at the end of the first course, even a positive spinal fluid was converted to negative by one such course of injections. We were not content to leave it at that, but 2 further courses were usually given. After a month's interval of rest a second course would start with 0·2 or 0·3 ml. and rise to 1 or 1·5 ml. for the twelfth injection using the same precautions as before. After another month's rest the W.R. of the blood was re-examined, and if the C.S.F. had previously been positive a lumbar puncture was repeated. As mercury is also a renal irritant it should not be given in any form to children having injections of bismuth, though with our earlier patients this precaution was not adopted which possibly accounted for albuminuria in some of the cases. With older children the dose of bismuth may be increased starting with 0·5 ml. and rising to 2 ml. or even to 2·5 ml. towards the end of a course in the case of children 12 to 14 years of age. The injections are given into the buttock region by the deep-subcutaneous or intramuscular route, as previously described. Particular care must be taken not to inject

[1] "Bisoxyl" (British Drug Houses) is a 10 % aqueous suspension of bismuth oxychloride with chlorbutol 0·5 %: 1 ml. contains 0·1 G. (100 mg.) BiOCl or 80 mg. bismuth metal. "Chlorostab" (Boots) is BiOCl in 5 % glucose and is supplied in two strengths: 0·2 G. BiOCl = 0·16 G. bismuth metal, and 0·25 G. BiOCl = 0·2 G. bismuth in 1 ml., that is double and 2½ times respectively the strength of bisoxyl. Other firms also market this drug.

bismuth preparations into a blood vessel, so that a correct siting and direction of the needle are essential and it is advisable to pull a little on the piston before starting to inject.

It has been mentioned that combinations of bismuth and arsphenamines (Bistovol and Bismarsen, Raiziss 1925) have been prepared bismuth and tryparsamide combinations have also been marketed. In our clinic we used to inject solutions of tryparsamide and suspensions of bismuth oxychloride together in the same syringe into the buttock region of children when the combined volume was not greater than 2 to 2 5 ml. The results were uniformly satisfactory

In older children and in adult syphilitics with cerebrospinal syphilis the larger doses of tryparsamide solution and bismuth suspension would be too bulky to give by intramuscular or deep-subcutaneous injection, and I have on several occasions seen necrotic abscesses of the buttock thus produced. In such cases the tryparsamide would be given intravenously and the bismuth intramuscularly or by the deep-subcutaneous route.

Toxic effects of bismuth We have given bismuth treatment to at least 260 patients either alone or in association with arsphenamines and tryparsamide by injection or acetarsol or mercury by mouth, and Table 33

TABLE 33

Toxic Effects (95) of Bismuth in 71 Syphilitic Patients out of 260 thus treated

Albumin and/or casts in first course	0[1]	
2. Albumin and/or casts in first course plus general susceptibility	1	
3. Albumin and/or casts in second or later course	30[2]	
4. Albumin and/or casts in second or later course plus blue-black line in gums	9	(50 with albumin)
5 Stomatitis and gingivitis	0	
6. Blue-black line in gums	5[3]	(25 with mouth lesions)
7 Anaemia (including 3 with albumen)	5	
8. Diarrhoea, fever or other symptom of overdosage or susceptibility	8	
9. Dermatitis	2	
10. General susceptibility (plus albumin)	1	
	9	
1 Died (after diarrhoea)	4	
	95	

[1] Includes 2 congenitally-syphilitic mothers
[2] Includes cases of acquired syphilis in children.
[3] Includes the 9 cases in group 4 and congenital mother
One died later of influenzal meningitis.

sets forth the toxic manifestations which we encountered, in addition to a small number of deaths attributable to the toxic action of the bismuth or to the disease itself The 71 patients who exhibited toxic manifestations included 3 congenitally-syphilitic mothers and 2 children with acquired

syphilis. It is seen from the table that the main toxic effects are on the kidneys (50 cases) and on the mouth (25 cases) Several of the children developed diarrhoea a few became febrile and showed other symptoms of susceptibility to or overdosage with the drug 5 showed varying degrees of anaemia and 2 only had skin lesions.

A boy of $3^{4}/_{12}$ years seemed to be susceptible to bismuth, for 4 days after the first injection of 0·15 G bismuth he vomited 4 times and had albuminuria. He was then given several courses of neo-arsphenamine without any reactions. At 8 years of age he was able to tolerate bismuth moderately well, but after the fifteenth injection of bismuth metal he had a dermatitis, first on the neck and later on the hands, which was attributed to the bismuth, since the arsphenamine treatment had ceased 21 months previously

The other case was that of a girl aged 5 years who so repeatedly developed a rash and impetigo on the face, ears and body when taking acetarsol that bismuth oxychloride was substituted. After the sixth bismuth injection the rash on the face recurred and there was a relapse of the impetigo. After a short rest the course of bisoxyl was resumed and completed without further mishap and the patient was able to tolerate 4 further courses of bismuth whereas acetarsol gave rise to repeated recurrences of the eczema and rash.

As has already been mentioned, the urine should be examined before every injection and if only a trace of albumin is present, its presence will be noted but the injection may be given. If casts are present in addition to albumin that week's injection is better omitted, after which injections can usually be resumed. Sometimes the kidneys are affected in the later stages of the first course of injections but usually it is in the second third or later courses that albuminuria occurs. There may be only a trace of albumin present, which may be disregarded, or there may be albumin + or + + even in the first course of a series which entails delay in treatment

Most of the cases of albuminuria ceased and cleared up spontaneously when treatment was discontinued and no permanent lesion of the kidneys seemed to follow In 2 patients a diagnosis of bismuth nephritis seemed justified One had haematuria, a temperature of 104 F followed by 4 days fever at 102 F yet when investigated 5 years later was regarded by Dr Payne, our biochemist as quite cured with normal kidney function tests and B P 118/70 The other patient had nephritis at 9 months and 6 months later was still passing much albumin but this had cleared and his kidneys were functioning normally at the age of 5 years.

The usual effect of bismuth on the mouth is the formation along the margin of the gums of a dark-blue line starting as a rule behind the incisor teeth This sign is not dangerous but is a signal for caution The teeth may need attention from the dentist and a peroxide mouthwash should be used. With continued injections the bismuth line may extend to the mucous membrane further afield and may then set up a gingivitis or stomatitis. Two of our severest cases of stomatitis followed upon the injection of bismuth metal which might be accounted for by the fact that

the preparation used was stronger than was realized or possibly that bismuth metal is more likely to cause gingivitis and stomatitis than is the oxychloride. Several of our children had diarrhoea and occasionally vomiting, but these symptoms are so easily provoked in young patients that it is difficult to say that they were attributable to the bismuth, though they seemed to be a contributory cause of death in the fatal cases.

Fatalities have been recorded from intravenous injections of bismuth in adults (Clarke Hughes, Johnson and others), and rarely exfoliative dermatitis has been a sequel of bismuth therapy This has to be borne in mind in the treatment of yaws in Africa and elsewhere when bismuth is employed on a large scale.

(E) General and special lines of treatment

The general paediatric treatment of the patient must not be neglected Whenever possible the infants should be breast fed, but if this is not possible the most suitable substitute food must be found for a syphilitic child should never be given to a healthy woman to be suckled.

General hygienic conditions, such as fresh air and suitable clothing should be attended to Between the courses of injections general tonics may be administered, such as syrup ferri phos. cod liver oil and malt extract, and vitamins A and D in appropriate doses should be administered to poorly nourished babies and infants. Should anaemia be present, reduced iron, 3–5 gr (180–300 mg) two or three times daily may be given together with ascorbic acid 50 mg every morning if upon investigation of the urine the patient is found to be deficient in vitamin C. In certain cases when the anaemia is refractory to drug treatment one or more blood transfusions—50 ml. 100 ml. 150 ml. according to the size of the patient and the degree of the anaemia—may be indicated. Thyroid medication to certain backward children in addition to the antisyphilitic treatment seems to be followed by improvement in some cases.

As has already been mentioned the disease appears nowadays to show certain mitigations in the severity of the symptoms as compared with 25 or 30 years ago Even at that time the local manifestations of the disease did not require any special treatment, the rash, for example, disappearing rapidly with the administration of mercury or Stovarsol or after a few injections of arsenic or bismuth. If many excoriations of the skin were present it was found beneficial to give the infant a boracic acid bath and gently dry it with a soft towel as a preliminary to treatment. The skin was kept as dry as possible and well dusted with a powder consisting of equal parts of starch, boracic acid, oxide of zinc and calomel This powder is also useful for dusting anal condylomata. To relieve the nasal catarrh—the cause of the snuffles—the nostrils should be mopped or irrigated with boracic acid or sodium bicarbonate lotion and then smeared inside with boracic ointment or weak ammoniated mercury ointment (1 per

cent in soft paraffin). This mercury ointment should also be used for sores about the mouth

In several of the foregoing chapters attention has been drawn to additional treatment on non-specific lines. The most important of these is perhaps the use of atropin as a routine measure in interstitial keratitis and to see that the pupil is thus kept fully dilated so as to prevent the formation of iritic adhesions. Other indications are the value of pyretotherapy and of cortisone in certain cases

At all ages intercurrent diseases should be appropriately treated with, if necessary a brief interruption of the antispecific therapy should this still be in progress.

Congenital neurosyphilis is the most resistant of all forms of congenital syphilis and it is for this aspect of the disease that most of the special lines of treatment have been evolved e g intraspinal therapy and pyretotherapy in their various forms. Our experience with these has been given in Chapter 8 In the past cases of spastic diplegia and paraplegia were frequently subjected to severe operations involving transplantation of nerves and tendons, without a thought for the condition of the patients nervous systems. These patients often had congenital neurosyphilis, some were already mentally defective and one has even seen a few who developed congenital general paresis during convalescence from the operation. In my view all patients with spastic para or diplegia should have a spinal fluid test before any operation is undertaken, and if the result indicates syphilitic involvement of the central nervous system and certainly in the presence of any mental deficiency I would strongly discountenance any reparative operation as being likely to damage still further the diseased central nervous system.

Children with latent congenital syphilis, that is to say those discovered to have a positive W R. during the routine examination of a known syphilitic family should be given treatment in order to safeguard them against the possibility of later manifestations of the disease.

(F) The follow up of the congenital syphilitic

Syphilis, whether acquired or congenital has always been a difficult disease to treat satisfactorily that is to say until such time as the attendant practitioner is satisfied that the patient can reasonably safely be regarded as cured. There have been and probably still are, some who think that a patient who has had syphilis never gets rid of the treponema. Perhaps the newer drugs which can destroy the treponema rapidly may have changed the outlook, but it will be many years before we are in a position to be dogmatic about the long-term value of penicillin and the schemes of treatment based upon it. In the meantime we must rely upon periodic examination of the patients as regards their physical condition and a blood test In order that this may be adequately carried out an efficient

follow up service is essential and in the words of H C and M H Solomon (1922) The value of a well run follow up service is nowhere greater than in this field namely concerning the value of treatment in congenital syphilis.

During my direction of the Clinic at Great Ormond Street (1917–1939) there was no follow-up service officially run by the hospital. If a patient defaulted from treatment for one week a letter was sent to the mother from my department and often this had the desired effect on the following treatment-day the mother then explaining that either she or the patient or possibly another child had been ill, so that she herself was unable to come. If one departmental letter was not successful a second one was sent and if this also failed a personal letter followed. It was sometimes found however that letters were unavailing and in such a case the services of the N.S.P.C.C. (National Society for the Prevention of Cruelty to Children) were enlisted for bringing the children to the clinic for treatment and periodic blood tests and for tracing defaulting families. When the patients reached adolescence and became more or less independent, follow-up practically always ceased since the patients had hardly ever been told by the mother why they had been coming to hospital sometimes for years. The remedy for this state of affairs is enlightenment and the education of the rising generation in sex hygiene stressing the importance of clean living of having a pre marital blood test and the value of antenatal blood tests for women in every pregnancy

The effects of treatment

It is remarkable how quickly syphilitic infants responded to treatment even by the old fashioned mercury method. We now know that although the symptoms cleared many of these patients were not cured, for they later showed the lesions of late congenital syphilis or were latent when they were discovered to have a positive W R. With the later methods of treatment, arsphenamines bismuth and penicillin the effects are even more remarkable and spectacular and the general constitutional improvement shown by the patients is often striking. In the past one frequently had the gratification of hearing a mother testify to the obvious improvement in her child's condition as the result of treatment. The two conditions in which there was no spectacular response to treatment were some cases of manifest neurosyphilis and of corneal lesions, but even here a favourable yet limited response could be expected in many of the patients.

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CHAPTER 13

ACQUIRED SYPHILIS IN CHILDHOOD

THE older syphilologists regarded acquired syphilis of infancy and childhood as an exceedingly rare occurrence and consequently thought it to be of no practical importance. It is true that authors reported isolated instances from time to time but until comparatively recent years the subject has not been seriously considered. It had long been my opinion that the various clinical forms which congenital syphilis is known to assume might be due to differences in the mode of infection, particularly intranatal and postnatal infection, with the treponema. This has already been referred to in the chapter on "Transmission." An explanation of the different types of congenital syphilis which are met in practice might be (1) a blood infection shortly before or during birth, (2) an infection of a hitherto healthy infant during its passage through an infected genital canal, and (3) an infection contracted in early childhood, from an adult or sib with syphilis in an infective stage. Waugh (1938), in a survey of the reported cases, was able to add 35 personal cases, 24 of them occurring in infants and young children up to the age of 11 years. Two certainly and a third probably acquired syphilis through sexual contact. The remaining 11 children varied in age from 12 to 14 years and all definitely became infected through sexual intercourse. Dennie and Polsky (1940) reported 12 personal cases, of which 10 were seen within the previous 2 years. Eisenberg, Plotke and Baker (1949) reported 20 cases of asexually acquired syphilis in children under 10 years of age from Chicago in the year 1947 alone. There is no doubt, therefore, that if the condition is borne in mind and looked for it will be found more frequently than it has been in the past, and that from an epidemiological and public health point of view this is an important aspect of the disease. Pernet (1917) during the first world war drew attention to the potentialities of the crèche as a disseminator of acquired syphilis, and all infants before admission to crèches should be carefully examined, including a W.R. after the age of 3 months.

It is essentially a syphilis of the innocent—syphilis insontium—and the chancre, if one be present at all is usually extragenital, and it may be so atypical or so small and the lymphatic gland involvement so slight, that it passes unnoticed at the time. Similarly the rash may be so

evanescent as to be easily and speedily forgotten, so that it is the exception *rather than the rule for the patient or the mother to have any recollection of* the incident. None of the 20 infected children reported by Eisenberg showed a primary lesion when examined in the clinic, but all showed a generalized *maculo-papular rash of secondary syphilis*, and all had positive serologies.

The occurrence of so many cases of late congenital syphilis in several recorded series including our own, some of which presented *lesions very analogous to if not identical with, the tertiary lesions of acquired syphilis* such as gumma of the palate with destruction of the soft tissues and nasal and palatal bones, suggested that these might be instances of acquired as opposed to congenital syphilis.

The following is a fairly comprehensive list of occurrences which might suggest that the syphilis of an infant or child was acquired rather than congenital (1) parents with negative W R. and no syphilitic history in the family (2) the patient being the only child in the family with a positive W R. (3) definite history of an infected foster mother wet nurse or attendant (4) infection in the parents *after* the birth of the patient (5) contact with a case of congenital or acquired syphilis in the infectious stage (6) history of a rash after vaccination circumcision or other minor surgical operation (7) the nature of the lesion for example necrosis or gumma of the palate, condyloma (8) history of sexual assault—and two features which might occur during the treatment of the patient (9) the occurrence of jaundice following arsenical treatment, which is very rare in congenital syphilitics and if it occurs rather points to the possibility of acquired syphilis in the patient and (10) the serological reactions which, as a rule, become negative much sooner in the acquired than in the congenital disease The erythrocyte sedimentation rate is generally raised sometimes considerably so in congenital syphilis and a normal rate would be in favour of the acquired disease.

There are two types of family which present difficulties one in which both parents are negative and there is one positive child not necessarily the eldest the other in which one or both parents are positive and one child, usually the eldest has a mild type of congenital syphilis usually in the form of interstitial keratitis. In the first type of family one must bear in mind the possibility of acquired infection from a source outside the family for example a nurse, a foster mother a wet nurse nursing home or other modes of infection to be described later In the second type of family the syphilis is an old or attenuated infection sometimes called the burnt-out variety which in my experience frequently occurred in the case of old soldiers or sailors who had served in the Far East or in India before the first world war The wife of such a veteran may become infected on marriage or at conception, but owing to the attenuation of the virus there may be no miscarriages, abortions or still

births, and the first child may be syphilitic but with only slight or even no infantile symptoms, yet suffer later on in life from *syphilis congenita tarda*

Wet-nurses Recognized wet nurses are practically a relic of the past and formerly it was not unknown for an infected nurse to infect a baby and so introduce syphilis to other members of the family Conversely a syphilitic baby infected a wet nurse and she in turn infected her own baby or others she might have been suckling The serological reactions no doubt can prevent a great deal of this mode of infection happening at the present time. In backward communities such events might still happen, or a friendly neighbour who is nursing her own baby might on occasion do the same to the infant of a friend and so possibly infect it. Instances of small outbreaks produced in this way are given by Bulkley (1898) Fournier and others. We have had a few cases in which the acquired syphilis was attributable to a foster mother but usually the evidence is circumstantial, unless the woman is known to have had either a syphilitic infant or a primary or secondary syphilitic lesion.

Infection in the parents since the birth of the child It is not always easy to fix the date of infection in the parents, but when this is possible, as we have done on several occasions, and the date is subsequent to the birth of the positive child, it is certain that this child acquired the infection after birth.

Infections from close contact In the chapter on transmission it was stated that the infectivity of congenital syphilis was not very great, but nevertheless instances were on record in which the disease had been transmitted from a syphilitic infant to adults coming into close contact with it. In this connection one must bear in mind the possibility of the transference of the disease by means of spoons, cups and other feeding utensils. It is a very common practice in this as in other countries for mothers and attendants to test the temperature and sweetness of the baby's food by putting a spoonful into their own mouth. Still has recorded a case where a grandmother a girl of 12 and a boy of 7 all became infected from a child 17 months old who had sores in its mouth The grandmother and grand daughter habitually fed the baby and the boy evidently became infected by using an unwashed spoon. They all suffered from ulcers or chancres on the tonsil

Another source of infection which is by no means uncommon is the habit which mothers have of moistening a handkerchief with their saliva to wipe off any food or dirt from their child's face and in this way chancres have been produced on the lip or other part of the child's face. It is similarly reprehensible thus to moisten a baby's dummy teat or comforter a device which is still all too frequently used, before inserting it into the child's mouth.

Kissing a child is another common practice which is liable to lead to the spread of infection. Here again the infection is nearly always on the lip

Infection by close contact with a parent suffering from primary or secondary syphilis has until recently been somewhat underestimated as a cause of acquired syphilis in children. This mode of infection is probably much commoner than is realized, and is stressed by Dennie and Polsky (1940) and Eisenberg *et al* (1949). There is no doubt that contact with bedclothes toilet and such like articles soiled with infective discharges may transmit the infection to others, and in not a few instances this seems to have been the mode of infection in some of our families.

Infections produced by minor operations Formerly when it was the practice to carry out arm to-arm vaccination there is no doubt that syphilis was sometimes conveyed in this way and the serum taken from a syphilitic infant doubtless gave rise to small epidemics of syphilis in the children vaccinated from such a source. Since arm to-arm vaccination has been prohibited the only likelihood of this small operation giving rise to syphilis would be in the event of the lancet used for scarifying the skin not being efficiently sterilized.

In connection herewith I may perhaps mention an interesting case related to me by a noted pathologist who told me that when he started carrying out Wassermann tests he used his own blood as a "negative" control, and to his surprise found that he did not give a clear negative On delving into his personal history he ascertained that when about 6 months old he was vaccinated from the arm of another child. About 3 months afterwards he developed various bone lesions, those on the tibiae giving rise to swellings which were still present when he recounted the episode to me, and another on the second metacarpal bone of the right hand which necessitated 2 or 3 incisions and left the index finger shortened. Syphilis as the cause of the lesions was not thought of at the time and therefore the disease was untreated His eldest child was mentally backward and he asked me whether I thought that his untreated latent syphilis might be the cause of the child's mental deficiency I replied that it was difficult to be dogmatic, but in view of the fact that there was no known mental deficiency in the family latent syphilis might quite well have been the cause of the condition.

Ritual circumcision is another small operation which has been instrumental in producing acquired syphilis in an infant. Amongst orthodox operators it was formerly the custom to promote bleeding from the cut surface by mouth suction and in that way syphilis was occasionally transmitted. Although mouth aspiration is I believe, no longer resorted to in this country it might still be so in orthodox communities elsewhere

It seems hardly necessary to stress the point that all instruments used for operations such as the removal of tonsils and adenoids, dental operations, etc. should be thoroughly sterilized, but I know of at least one case (adult) where a patient contracted the disease from an infected dental elevator "

Tattooing may be a cause of infection, and I well remember the father of one of my patients who was tattooed literally from head to foot and had

a positive W R who solemnly stated that he had never had connection until marriage and whose syphilis I attributed at the time to the tattooing operation.

Many other possible modes of infection under this heading are given in the Solomons book (pp 191–193) some of which may be applicable to children.

During the study of the 900 cases of congenital syphilis and the further 110 probable and possible cases of the disease, nearly 50 cases of undoubted or probably acquired syphilis in children were discovered which, if the diagnosis is correct in all the cases, would give the ratio of congenital to acquired syphilis in children as about 20 to 1 In the earlier stage of the author s experience, acquired syphilis in children was not considered to be of much practical importance and consequently inquiries were not so searching as they might have been or as they afterwards became The various grounds upon which the diagnosis was based in each case have already been given, and it only remains to add that the degree of certainty ranged from 100 per cent in cases in which for example a sexual assault was made upon a child or in which the only syphilitic sib in the family had been put out to nurse and had in that way become infected, down to 25 per cent in other cases The point to be emphasized is this in a case of what appears to be congenital syphilis where the history or the investigation of all the members of the family discloses some unusual feature, e.g a youngish mother has a negative W R whereas the child is positive and especially if this child is the only positive one in the family the probability of acquired syphilis should be borne in mind and every endeavour should be made to unravel the mystery This should be done to protect the mother and other members of the family from acquiring the infection and, by keeping a watchful eye on the mother during any subsequent pregnancy to protect future children from the infection.

In analysing our 18 cases of presumedly acquired syphilis we find the method of acquiring the disease to have been distributed as follows In 12 cases the infection seemed to have followed home contact such as close personal proximity infected towels flannels and so forth and infected eating utensils, forks, spoons, etc. In 3 cases the patients were probably infected by a foster mother or by being put out to nurse 1 case was undoubtedly acquired sexually 1 was attributed to the use of a rectal syringe, and 1 was attributed by the mother to the child sitting upon a public lavatory after a local injury to the buttock.

All but two of the cases had completely negative spinal fluids one of the exceptions had a negative W R. in the fluid but 30 cells per ml at the first investigation and 3 cells when examined a few months later the other had a Lange curve 1233210–0 which was negative 6 weeks later Eight of the cases were latent when seen in the clinic but of these 1 had

previously complained of a sore mouth which may have been the primary lesion and 2 others had had a rash, doubtless syphilitic, shortly after the disease had presumedly been acquired. A brief account of the individual cases is as follows

1 C B female, born 1921 had no infantile symptoms and was a latent syphilitic when examined routinely at 4½ years. A negative sister was born in 1923 the mother was infected in 1924 and a congenitally-syphilitic brother was born in 1925 from whom or the mother C.B became infected.

2. C.B., male born 1914. No infantile or later symptoms. Father infected after birth of patient. W R. became negative in little over a year Suffered from Clutton's knees at 10 years of age

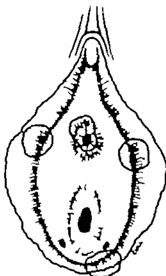


Fig 93 Venereal ulcers on the genitalia of a child aged $4^{10}/_{12}$ years, who had been sexually assaulted a short time previously They are primary lesions not condylomata (9, 8 G)

(*Courtesy Dr Mary Shaw*)

3 S.C., female, born 1916. Mother infected 1918. No infantile symptoms but had osteo-periostitis of tibia at 8½ years. The W R. became negative in a little over 2 years.

All three cases were regarded as being due to infection by home contact

4. S C. female born 1917 Illegitimate and put out to nurse with foster-mother who was thought to have been syphilitic. The child had a circinate rash on the thigh and vulva at the age of $1^{7}/_{12}$ years which lasted a month Her W.R. was then found to be positive but the mother's was negative The blood W R. took nearly 3 years to become negative, which is rather longer than the usual time we found in the acquired cases and which may have been due to irregularity in attendance for treatment.

5. D M female, born 1921 Mother had primary and secondary syphilis 3 months after the birth of the child, and since she was suckling the infant it developed a sore mouth which may have been a primary lesion possibly acquired from infected milk. The disease was latent at 3½ years. The patient had no subsequent symptoms except vague rheumatic pains, but the W R. remained positive for several years, doubtless because treatment had been very irregular

6. E.W., male born 1912. No infantile or later symptoms until the age of 7 years. Then the boy had condylomatous lesions round the anus, alopecia and enlarged posterior cervical glands. The mother and two brothers gave negative serological tests, and the case appeared undoubtedly to have been an acquired one. The mother ascribed it to syringing the boy for worms, although she definitely stated that she bought the syringe especially for the purpose Be that as it may the origin of the infection remained obscure.

7 C S., mentioned on p 4?6.

8. P B. female born 1937 had no infantile or later symptoms of syphilis but was discovered to have a positive W R. when she was tested for the gonococcus complement fixation-test (G C F T). The father had a sore in the mouth which

was either a chancre, a mucous tubercle or possibly gummatous ulceration. The mother's W R. was negative on 2 occasions, but her blood gave a positive G C.F T

9. S.G female, born 1928, had no symptoms until she was sexually assaulted at the age of $4^{10}/_{12}$ years by a lodger in the house. The mother and father had negative blood tests and 5 brothers were all healthy The patient had four small ulcers on the genitalia (see Fig 93) and shotty enlarged inguinal glands. Shortly afterwards she developed moist patches, probably mucous tubercles, at the angles of the mouth. Her W R. became negative in 3 months.

10. M.S., female, born 1935 had no infantile symptoms. The history given by the mother was that the patient sat on a rusty nail when about 1½ years old and that a "rash came and went." At the age of $2^4/_{12}$ years the lesion started as a pimple on the right side of the anus, and when seen and photographed a fortnight later (see Fig 94) there was a mass of condylomata to the right of the anus, in scrapings from which the *T pallidum* could be demonstrated. A few days later there was a gluteal ulcer probably a "secondary" manifestation, the right inguinal glands were enlarged, and inflamed patches were present on the fauces, tonsils and soft palate suggestive of a syphilitic sore throat. X rays showed no periostitis. It is difficult to say how the disease was acquired in this patient, but the mother attributed it to sitting on a public lavatory The blood W.R. remained positive for about a year The child subsequently at the age of $4^4/_{12}$ years, developed poliomyelitis and lost the power in her left leg and hip girdle.

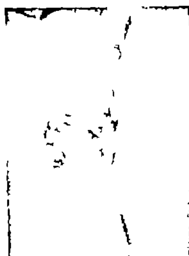
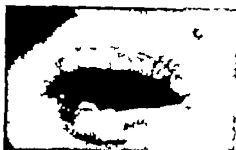


FIG. 94. Syphilis acquired by a girl at about 21 months of age. At the age of 2¼ years there was a mass of condylomata to the right of the anus and shortly afterwards the gluteal ulcer and syphilitic sore throat (secondary manifestations) arose

11 V J., female, born 1931 She was a healthy baby but came from a neglected home, 2 older girls having scabies when the patient was seen in Feb 1936. The mother became infected in Nov 1934 and was treated at a general hospital under Dr McElligott. The child had a sore in the genital region some months after the mother was infected, and the condition was described by her as if the child had been chafed by tight clothing A few weeks later the sore on the upper lip appeared. At the age of $4^2/_{12}$ years she was admitted to our clinic from the general hospital she and her mother had been attending with the diagnosis of ? late secondaries. The accompanying figures show the condition on admission namely extensive ulceration of the skin of the left vulva and buttock which had been present for about 2 months, and a similar but smaller lesion on the right labium majus anteriorly (Fig 95*b*) That on the buttock was several inches long by 2 inches wide (8 × 5 cm) and that on the labium 1 inch long by ¾ inch wide (2 5 2 cm) The inguinal glands were slightly enlarged and shotty The child was dirty and neglected and the ulcers were possibly secondarily infected. Diphtheria or tubercle were suggested as possible

diagnoses of the local condition by our dermatologist. There was also ulceration on the left side of the upper lip which had been present for about 7 weeks (Fig 95a) the cervical glands were not enlarged. The ulcers had a sloughy base and there was a little induration of the edges. No treponemata could be demonstrated either by the dark ground or by Leishman's stain in serum from the ulcer on the right labium majus, but the mother's positive history of syphilis



(a)



(b)

FIG 95 Mucous tubercle of lip and secondary ulcers of the buttock and right labium majus in a girl aged 4 years the result of syphilis acquired from the mother at about the age of 3 years The mucous tubercle had been developing for 7 weeks before the patient was seen in our clinic

and the child's W R. being found positive, the lesions were regarded as being late secondaries, the child having become infected shortly after the mother in Nov 1934. The lesions healed quickly under antisyphilitic treatment, and the patient was shown at a lecture-demonstration at the age of $5^{8}/_{12}$ years with a big scar on the buttock and adjoining area and a well marked scar on the lip. The W R. quickly diminished in titre and in 9 months was nearly negative but it did not become quite negative until 2 years after treatment was begun.

While the family was under observation the other sisters did not become infected.

12. S.H. male, born 1915 Illegitimate and put out to nurse. His mother's W R. was negative and he was the only positive sib in the family His W.R. became negative in about 18 months and his C.S F was negative. He was brought to the hospital on account of I K. at the age of $6^5/_{12}$ years.

13 and 14. The next two cases were sisters born in 1913 and 1914. Neither had any infantile symptoms. The elder girl (D W) is said to have had fits when teething and until about the age of 4 years. The younger one (V W) had no infantile symptoms but at the age of 4 months is said at a children's hospital to have had an enlarged liver At the age of 7 years, however when seen by us, she was a case of latent syphilis. Both sisters were examined routinely when their younger brother born 1917 was found to be suffering from frank congenital syphilis, and all the evidence seems to point to the sisters having acquired the disease as a home infection when the brother was a baby They both had negative C.S.F s and the blood W.R. was negative, in the one case after nearly 2 years treatment, and in the other case after only one course of neo-arsphenamine.

15 The last case of this kind was that of a girl (Irene W), born in 1921, who at the age of 5 years had a rash on the buttocks with copper-coloured staining This seems undoubtedly to have been a syphilitic rash which was the result of an acquired infection from the baby sister who was about 4 years her junior (see I W., p 130).

The other 29 cases in this group are called doubtfully acquired, because the probability that they were acquired is not so strong as in the cases just recorded. Details of some of these cases will be briefly given.

16 Fred H., born 1918. The mother was infected early in pregnancy and was treated with mercury and 8 injections of neo-arsphenamine. The baby suffered from no infantile symptoms, so that he was probably protected from uterine antenatal infection by the treatment the mother had received. At the age of 11 months he was an inpatient at the London Lock Hospital with perianal condylomata, but we have no further record of his W R. or treatment. He was examined routinely in 1923 when his baby sister was found to be syphilitic. The W R. was then strongly positive and it remained positive from the age of 4½ until 8 years. The C.S.F was negative. He was probably born healthy and either had congenital syphilis with delayed symptoms or acquired the disease from his mother and showed the perianal lesions in consequence. This case illustrates how difficult it is to decide between a delayed congenital infection and one possibly acquired.

17 Kenneth G., born 1926, had no infantile or later symptoms until he was 4 years old when there was a history of haematuria lasting 1 week. There was no oedema. At that time a sister was born who suffered from frank congenital syphilis, and when the patient himself was examined he had no symptoms, except some anaemia and debility but his W R. was strongly positive. We have no information about the father but he may have been undergoing treatment for syphilis at the time, which may have caused the infection in the boy to be a very mild one, or alternatively the boy's infection may have been acquired as a home infection from the baby sister The latter alternative is rendered likely by the fact that the W R. became negative within 6 months, after about 20 injections of bisoxyl which, at his age (4½ years), would suggest an acquired rather than a congenital infection.

18. Arthur W., born 1 month prematurely in 1930, had "ulceration round the mouth" at 3 months and some ulceration round the anus (? condylomata) at 2 years. He was admitted at the age of $4^{4}/_{12}$ years to our residential congenital syphilis clinic from a children's hospital with the diagnosis of "Clutton's knees (?)" of 2 weeks duration (Figs. 74 75) On admission he had a big bossed head, with rhagades of the lips and at the angles of the mouth, and was thought to be somewhat mentally deficient. He had been a patient at yet another children's hospital where at 3½ years he had inflammation of the eyes, which was thought to be due to phlyctenular conjuctivitis. No blood test was carried out. The child is said to have kept his eyes closed for 6 weeks, after which they improved for a time and then relapsed at 4 years, when they were red and painful for a month. The eye condition might have been I K. and at first sight the patient seemed to be a probable congenital syphilitic. The patient's parents and 3 sisters, however all had negative serological reactions, so the diagnosis was by no means easy The C.S F was negative at 4½ years, the sedimentation rate was normal and the W R. strongly positive The X rays of the knee joints at the age of 4½ years showed swelling in the joints with slight rarefaction in the epiphyses. There was also periostitis of the shafts of the femora and possibly of the tibiae. Two later radiological examinations of the joints showed definite irregularity of the epiphyses, suggesting a chronic arthritis, and in addition there were horizontal lines of calcification with thickening of the compact bone of the femur which was interpreted as being evidence of a chronic osteitis. It is seen therefore, that the joint lesions were definitely unusual and not like the ordinary "negative" appearances shown by the typical Clutton's joints. He afterwards went down to live in the country and owing to the world war we had no opportunity of seeing him after 1939 The last report received about him was that he looked and felt well, his teeth were poorly developed but showed no Hutchinsonian or Moon's characteristics. There had been no relapse of the I K or of the arthritis (1939).

19. Lettie K born 1915 had no infantile symptoms. She has already been referred to on p 181 where it was pointed out that her W R. was discovered to be positive on doing routine tests on nephritic patients. Her syphilis may possibly have been acquired and not transmitted by the mother transplacentally in the usual way which might account for the unusual clinical and serological manifestations the patient exhibited

20 Joseph K born 1925 had no infantile symptoms but is said to have had inflammation of the bowels at 4 years, when he was not seen by us. At the age of 11 years he developed an ulcer on the leg, for which he attended the skin department of another hospital and although he attended for 5 months syphilis as a possible cause was not suspected. It was only when a younger brother was brought to us with frank congenital syphilis that Joseph, at our request came for investigation. *His blood was found to be strongly positive so that the* ulcer of the leg was doubtless gummatous in nature. His teeth were normal in appearance and the diagnosis lay between latent congenital and acquired syphilis. The latter is highly probable because when the boy was 4 years old a sister was born who developed typical congenital syphilis, and it is quite likely that owing to the conditions under which they were all living the boy acquired the disease

In addition to the above there were undoubtedly other cases which might legitimately be included in this category as for example the C family of which a brief account was given in Chapter 1

Family "G" No. 705. The father is stated to have had primary syphilis just after the end of the first world war and to have had 2 years' treatment at a general hospital (X). He was discharged "cured" from hospital X, and 15 years later at hospital Y his blood W. R. was found to be negative. The mother who was 16 years his junior is stated to have had secondary symptoms 3 months after marriage for which she was given 6 months' treatment at hospital X. When her blood was examined at hospital Y in 1933 it was found to be strongly positive. The issue of the marriage consisted of 7 children:

(1) Girl, born 1926, who is stated to have made slow progress as a baby. She must have had fairly severe ulceration round the mouth, as the lips were all scarred, particularly at the angles, so that the mouth was very small (microstoma), and when we saw her at the age of nearly 9 years she could with difficulty open her mouth and then not widely enough to show her Hutchinsonian teeth. Two plastic operations were performed to enlarge the mouth, but the results were not very satisfactory. At first she was spiteful to the other children in the residential clinic, but later, when she had received some treatment and was given more responsibility, she became quite useful in looking after the smaller children. It was thought possible that her spitefulness might be a symptom of an otherwise latent neurosyphilis, but investigation of the C.S.F. did not bear this out.

(2) Girl, born 1927, was a healthy baby and did not suffer from any symptoms at any time. Her W. R., however, was strongly positive at 7½ years (latent syphilis).

(3) Boy, born 1928. Also had no infantile symptoms, but on admission to the residential clinic, at the age of $5^{11}/_{12}$ years, he had a violent temper and was thought to be somewhat mentally defective. He had a squint and on examination of the fundi granularity was seen. The boy improved under treatment and the discipline of the clinic and it was then considered that he was not mentally defective. He was given intensive treatment with arsenicals and mercury alternating with bismoxyl for more than 3 years, but even at the end of that time, when his parents insisted on taking him home, his W. R. was not negative (? latent syphilis).

(4) Boy, born 1929. No infantile symptoms and at the age of 5 years he seemed quite well except for bow legs and his W. R. was negative.

(5) Girl, born 1930. No infantile symptoms but was bow-legged when seen at the age of 4. Her W. R. was positive (latent syphilis).

(6) Boy, born 1931. No infantile symptoms but at the age of 3 was also bow-legged and rickety and had a negative W. R.

(7) Boy, born 1938. Born after mother had had further treatment at hospital Y mentioned above. This child was not seen by us, so that we have no record of any symptoms, but he died at the age of 5 months of "bronchopneumonia."

This is an interesting family history because the parents are known to have had primary and secondary syphilis for which they were given treatment *inadequate for their cure but sufficient to mask symptoms of syphilis in any of the children*. They were nearly all cases of latent congenital syphilis, unless perchance one or more of them may have acquired the disease. All the conditions for the spread of the disease in a non-venereal manner were present in the case of this family, which was very poor, badly housed, and, as the record shows, producing a child nearly every year. It is seen that there were at least 4 cases of syphilis amongst the children, the last one occurring between two negative children.

TABLE 34

Symptoms exhibited by 47 Children with Acquired or Possibly-acquired Syphilis

Latent	18
Condylomata	8
Rashes	6
Interstitial keratitis	4
Joints	2
Local ulceration	2 (including one sexual assault case)
Osteo-periostitis of the tibia	2
Ulceration of palate and nasopharynx	2
Gummatous ulceration of the leg	1
Fissured condition of skin of vulva	1
Anaemia and malnutrition (after chancre on the lip)	1
Neurosyphilis with empyema (child of a congenitally-syphilitic mother)	1

In addition to the above symptoms which were noted at the time the child was examined, 5 cases showed jaundice during treatment and one additional patient appeared to be slightly icteric after one injection With rare exceptions in which the records were indefinite or incomplete none of the patients in this category showed infantile symptoms, and rather more than one third of them were latent when the blood was tested. The commonest lesion was condyloma, and it is important to emphasize that the exudate from condylomata swarms with treponemata so that if the same towel or cloth be used on a healthy child after an infected one infection can easily be spread in this way In one case that came to our notice a mass of condylomata had been missed for a period of several months, thus giving ample opportunity for the spread of infection. Among the rashes described were (1) a case thought to be food poisoning at 18 months, (2) a circinate rash on the thigh at 19 months, (3) a rash on the buttock with coppery staining at 5½ years (4) a rash in two brothers at 1 and 4 years of age respectively shortly after their mother and baby sister had a rash, and lastly (5) one patient, case 11 who had a skin lesion which was regarded as being a late secondary manifestation

It is interesting to note that in no case did we find a primary lesion and this concurs with the findings of Eisenberg *et al* who stated that in *none of their 20 children was a primary lesion found* but they were more fortunate than we were, in that they were able to see a generalized maculo-papular rash of secondary syphilis in every case There is no doubt that ***we have here an important mode of spread of syphilis in an asexual manner among children of poor ignorant parents*** who may be living in overcrowded homes and under unhygienic conditions It behoves the physician in charge of adult patients who are in an infective stage to point out the risks run by individuals especially children with whom the infected adults come into close contact and the epidemiologist and public health authorities should take note of these serious possibilities

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CHAPTER 14

SYPHILOIDS

It has been recognized for many years that in various parts of the world certain diseases occur which bear a strong resemblance to syphilis in symptomatology serological reactions and their response to the usual antisyphilitic remedies. These diseases are variously named in different countries as yaws, bejel, pinta and many others less well known and it has been a matter of speculation as to the relation between these various syphiloids and true syphilis A treponema has been described in several of these conditions, which are consequently grouped under the heading Treponematoses.

Many authorities regard these different treponemata as different species but others think they are merely strains or varieties of a single parasite. Hudson (1946) strongly supports the view that the various diseases which can validly be ascribed to the action of a treponema are but various manifestations of the same disease, and his monograph is entitled Treponematosis and not The Treponematoses," thus emphasizing his point of view He ardently advocates that the syndromes which are usually described as different but allied diseases under the heading of yaws, pinta bejel etc really have a closer relationship and that they are due to a single species of treponema, *T pallidum* the parasite having changed in its habits through long years of adaptation to external factors, such as clothing cleanliness and other effects of civilization upon its hosts, and local environmental conditions such as humidity and changes in temperature in the particular locality Hudson gives an interesting and exhaustive account of the various diseases known, or presumed to be due to a treponema and brings forward strong evidence in support of his thesis. This is that Treponematosis is a universally distributed disease caused by *Treponema* a genus with one species *pallidum* This disease presents different clinical patterns under different climatic and sociological conditions Treponematosis (yaws) is an ancient disease of man, which probably spread from an origin in Africa Syphilis and the syphiloids—yaws, bejel pinta njovera irkintja (*of the Australian aborigines*) *etc.* are but different clinical entities of the same disease

Yaws[1] (Framboesia)

This disease has been known for a very long time as being predominantly a tropical affection occurring in Central Africa Burma, the East Indies, the Pacific islands and the West Indies. Hudson regards its primitive origin to have been Central Africa, where it existed as a childhood disease, non venereal in origin, and affecting everybody in the primitive villages. It started with a florid skin eruption and ended in gangosa pinta-depig mentation skin ulcers and periosteal gummata. When the disease spread across the world, and particularly as with the march of civilization man became washed and clothed, the treponema changed its habits, and treponematosis as an exanthem of childhood became less prevalent. The treponema found climatic and environmental conditions unsuitable for its survival and as Hudson says being a versatile parasite, it merely changed its angle of attack from a pattern of juvenile non venereal disease to one of adult venereal infection. In this manner intermediate forms and syphilis itself developed and, later the childhood non venereal and the adult venereal forms existed side by side. If Hudson's view of the oneness and universality of treponematosis be correct, the statement of Christian (1946) that regions in which yaws is endemic must be considered as so many reservoirs of world infection exactly as are foci of malaria and yellow fever assumes tremendous importance for the epidemiology of syphilis.

Bejel

This disease, affecting Arabs in the valleys of the Tigris and Euphrates and the adjoining regions of Mesopotamia and Syria, was first described by Hudson in 1928 It is due to a treponema indistinguishable from the *T pallidum* of syphilis and in the main it resembles syphilis both in its clinical and serological manifestations and in its response to treatment Hudson writes The clinical course of bejel is briefly as follows. At some time in early life the Bedouin child contracts bejel from some other child in the acute stage of the disease. The spirochaete usually is passed *from host to host by immediate, non-sexual contact, and the transfer is* favoured by general uncleanliness, total lack of segregation and the succu lence of the mucocutaneous lesions. Possible auxiliary factors in con tagion are the use of a common drinking bowl, the habit of kissing and fondling children, and the presence of the domestic fly the louse and the flea. Lesions often appear first in the mouth, but are soon followed by moist papules in the folds of the skin and by drier lesions on the trunk and extremities. Treponemata are easily demonstrable in great numbers

[1] Hudson says (p 52) In 761 d Sauvages described yaws in Africa as disease in its own right thus signalizing differentiation which persists to this day

in these lesions. A roseolar eruption has been observed but is rare. Late lesions consist of ulceration and erosion of palatal and nasal bones which involve pharynx and often the larynx, gummata of skin and subcutaneous tissues producing huge ulcers and cicatrices, *osteoperiostitis, particularly* of the long bones, with formation of sabre shins, adenopathy juxta articular nodules, hyperpigmentation depigmentation hyperkeratosis and alopecia. An adult who has escaped bejel in childhood is likely to contract it later from a child, often his own. The course of the disease in the adult does not differ essentially from that of the child. Hypertension is virtually unknown in the Arab and is exceedingly rare. Bedouin women who have had bejel do not ordinarily transmit it to the fetus; abortions and miscarriages are not more frequent among them than among neighbouring groups of women.

Hudson further remarks that "Bejel is indistinguishable from yaws in many of its manifestations and that both diseases tend to disappear rapidly when individuals are brought into contact with *civilizing influences*. On the other hand bejel is indistinguishable from syphilis in the fact that the mucous membranes are constantly involved in the early stages, in occasional alopecia, in many of its general pathological aspects and its occurrence outside the tropics. There is in effect, no clear-cut difference between bejel and yaws or bejel and syphilis. It is a variant of treponematosis, one of those transitional forms which prove the essential oneness of this versatile disease of man."

In 1934 MacQueen published an account of syphilis insontium in Palestine which appears to be the same as the condition bejel previously described in Mesopotamia and the Syrian Desert. Both Hudson and MacQueen point out that the Arabs attach no shame to the disease as it is practically always spread non venereally and is not associated with gonorrhoea.

Njovera

Recently Willcox has made a study of this disease in Southern Rhodesia. He regards it as an endemic syphilis which is apparently indistinguishable from bejel and like it, is usually contracted in childhood. The question whether the cardiovascular and nervous systems may be involved in these non-venereal forms of syphilis must still be considered *sub judice*. Willcox remarks that yaws may coexist with njovera, but he explicitly states that if Hudson's theory of treponematosis is accepted and that yaws and syphilis are really one and the same disease modified by racial climatic and sociological conditions, and primitive yaws becomes venereal syphilis *as the only hope of survival for the treponema* with intermediate forms still present as bejel then we may have here instances of the transition in progress.

The problem of the treponemal infections and, in particular the possibility that the non venereal form may act as a reservoir from which the venereal form can be reinforced raises a point of the highest importance in the epidemiology of syphilis. Since also it concerns health and well being as well as socio-economic conditions (including general education) among the less enlightened races it is undoubtedly a problem needing attention, which it is in fact, receiving under the aegis of the United Nations Health Organization. Since, however in *endemic syphilis* which exists as pockets of treponemal infection in Jugoslavia, various parts of India and Africa and elsewhere in the world, the congenital form is very rare, this variety of the disease cannot be discussed here. Apart from mass treatment, to be carefully followed up later which is being carried out as widely as possible and which may result in a marked reduction in the number of infections the two most interesting fields for research are (1) the identity of the causal parasites in the different forms of treponematosis and (2) the immunity reactions of animals and humans infected *by one strain of the parasite to infection by another strain.* Future administrative action would be determined by the outcome of such research.

Hudson's thesis appears to have much to commend it, because it would seem to be supported by the writer's own experiences. During 50 years he has seen remarkable changes take place in work on the natural history of diseases An example is lobar pneumonia, which was a very common disease at the end of the last century with its characteristic symptomatology and its sudden termination at the end of 8 days, in most cases by crisis, but which is much more rarely seen to-day than it was at that time. Scarlet fever which then attacked most children, very often severely was in many cases succeeded by renal complications and sometimes by lesions of the cardiovascular system which are rarely seen to-day in fact this severe variety of the disease seems to be almost dying out. Not only are diseases changing but the causes of disease themselves seem to be undergoing evolution I have held the view for many years that the bacteria which give rise to different diseases are changing Originally I was interested mainly in the intestinal organisms giving rise to gastroenteritis and different forms of dysentery in children, and as long ago as 1923 I suggested that *these organisms were in a state of unstable equilibrium* and that they might even have changed their biochemical and other attributes under observation I pointed out that this was hardly to be wondered at as these lowly organisms multiply about every 30 minutes, and in the intestine their pabulum is constantly changing in composition as well as in *p*H In the circumstances it would be more surprising if the parasite always retained the same characteristics than that it should change them

These views were not accepted at the time and one critic pointed out

that the diphtheria bacillus had not changed since Park introduced special strain for the development of antitoxic sera. We now know t there are at least three varieties of the diphtheria bacillus—mitis, int medius and gravis (McLeod 1950). Furthermore, since 1923 a good d of work has been done upon the varieties of streptococci pneumococ intestinal pathogens, etc. which, in my view points to a condition , instability or mutability of these organisms, and I therefore believe tl diseases, as well as their causative agents, may be in a constant state flux Syphilis itself has changed within my own recollection. In the ye 1899 I saw in hospital in Shanghai among the British soldiers station in the Far East, several cases of rupia with the limpet shell lesions near an inch above the surface of the skin. Such severe syphilitic lesio are practically never seen in this country to-day and in the intervenir half-century I have seen rupia once only This change may be dt partly to changes in the virulence of the parasite certainly to moder *methods of treatment and possibly to changes in habits and customs an* to race immunization. Hudson s view that venereal syphilis has evolve from non venereal treponemal parasitism has much to commend it, an even though he may not have originated the idea, he has courageoush championed it in his interesting monograph.

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